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THE AMERICAN ACADEMY OF NEUROLOGY

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Volume 11 - Number 12

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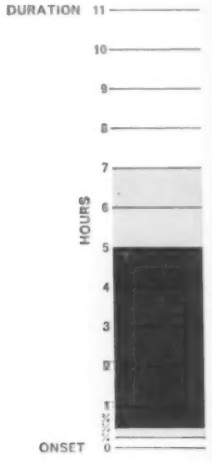

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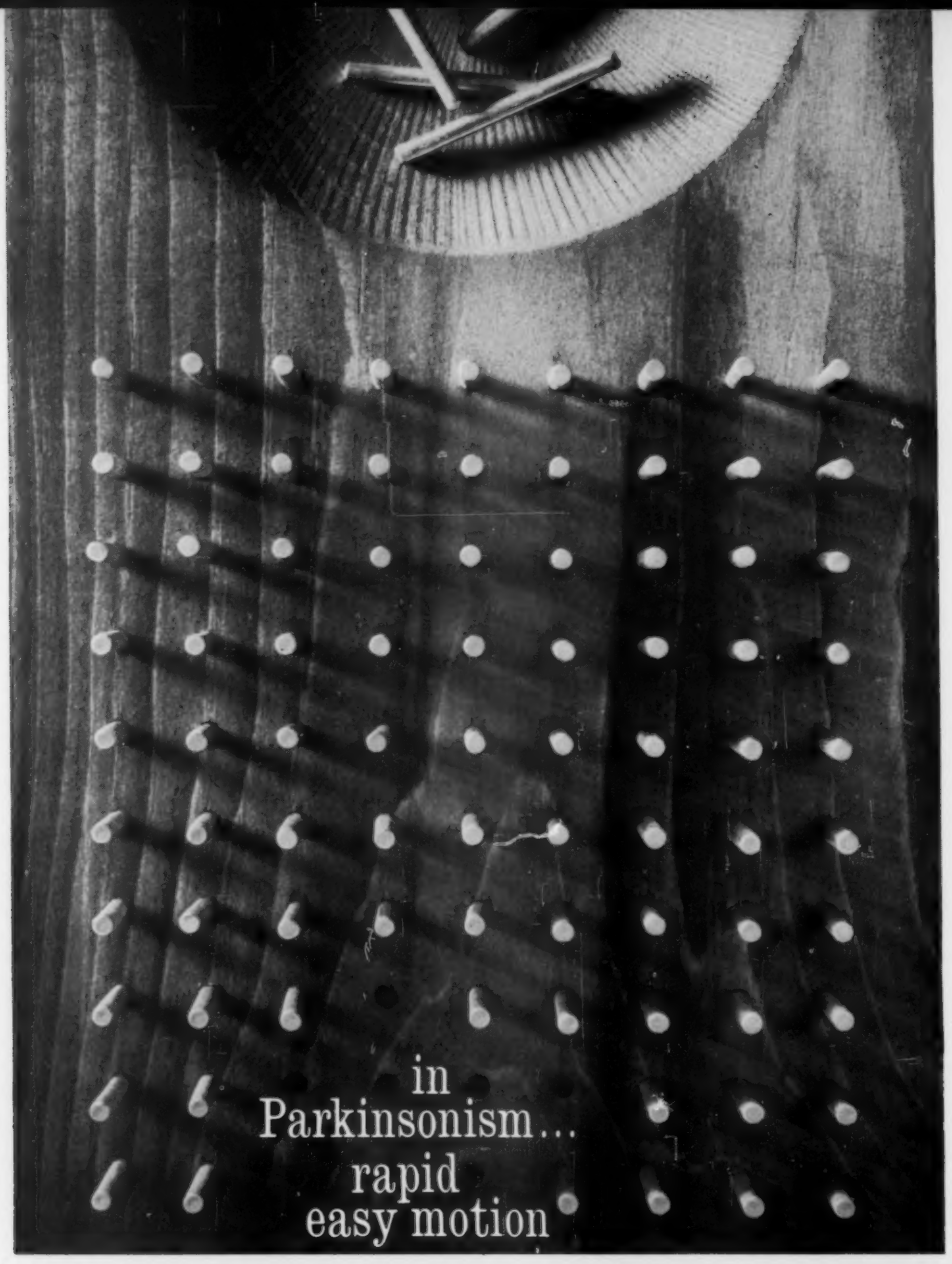

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NEUROLOGY is published monthly at 84 So. Tenth St., Minneapolis 3, Minn., by LANCET PUBLICATIONS, INCORPORATED. Subscription rate: $12.00 a year, $1.00 a copy; outside the United States $13.00 a year, $1.10 a copy. Second-class postage paid at Minneapolis, Minn.

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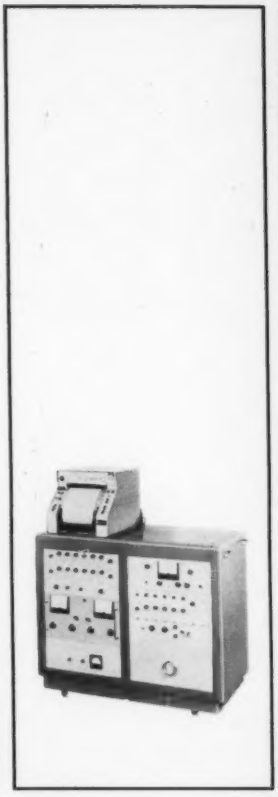

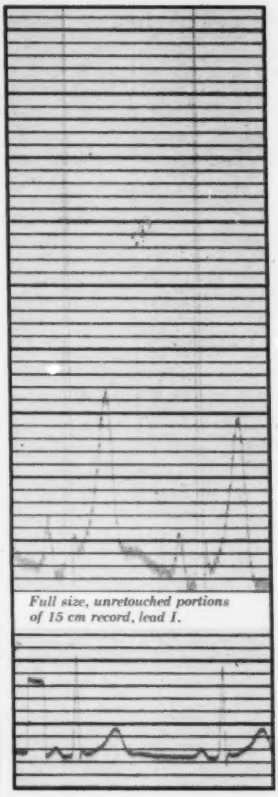

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Neurology Volume 11 • Number 12

Heredofamilial neuritis with brachial predilection

J. C. Jacob, M.B., B.S., Frederick Andermann, M.D., and J. Preston Robb, M.D.

FROM TIME TO TIME, one sees patients with isolated peripheral nerve palsies for which no apparent cause can be found. Inquiry may reveal that other members of the family have had similar conditions.

We have recently studied 7 patients, members of 2 unrelated families, who have suffered single or recurrent episodes of peripheral nerve palsies. In 1 family, the episodes were characterized by the onset of acute pain followed by severe weakness and wasting, as well as reflex and sensory changes in the distribution of the involved nerves or roots. In this family, the branches of the brachial plexus were usually involved, though involvement of the lower cranial nerves, lumbar plexus, and peripheral nerves was occasionally seen. The patients recovered useful function with minimal residual deficits. The tendency to such recurring episodes in this family appears to be genetically linked with dwarfism and a peculiar physiognomy. In 3 members of the second family, similar episodes are recorded, some of which consisted only of peripheral nerve palsies.

Attention was drawn to this syndrome in a recent paper by Taylor,[1] who described 24 members of a family afflicted with single or recurrent bouts of mononeuritis multiplex or brachial neuritis. The first report in the literature of similar cases is that by Dreschfeld[2] in 1887, who discussed in a series of papers some of the rarer forms of muscular atrophy. One of the patients described was a 43-year-old woman who had borne 12 children. She "felt a quick and shooting pain across her right hand, which was especially severe over the little and ring fingers. Very shortly after this, the wrist dropped and soon she found her arm also paralyzed, the shoulder being more affected than the elbow; the whole arm was very painful. Fourteen days later, the left arm became attacked; here also pain in the ring and little fingers was the first symptom and this was followed by wrist drop and paralysis of the arm and shoulder, with great pain in the affected part and pain across the shoulders from side to side." She had marked atrophy

From the Department of Neurology and Neurosurgery, McGill University, Montreal, and the Montreal Neurological Institute.

Presented at the thirteenth annual meeting of the Canadian Neurological Society, Montreal, June 1961.

and paralysis of the muscles of the fingers and hand, as well as of the extensors of the fingers and wrist. The muscles of the arm were likewise affected. No distinct anesthesia could be made out. She recovered completely over a period of some months, but, two or three years later, similar attacks of pain, paralysis, and atrophy developed. The patient's sister had a similar attack at the age of 25 with severe pain between her shoulders and hand wasting and weakness. At the time of the report, she had had 7 similar attacks. Initially, Ross diagnosed syringomyelia. Dreschfeld, however, suggested to Ross that this was a peripheral neuritis. These 2 sisters were independently reported both by Dreschfeld and Ross and Bury.[3] It is hard to improve on Dreschfeld's description of this syndrome at the present time. We are also not much further advanced in understanding the etiology of this condition, and Dreschfeld's comment is interesting in this respect: "There was no suspicion of alcoholism in this case nor anything pointing to lead intoxication—and I therefore look upon it as a case of so-called rheumatic peripheral neuritis; the onset, the pain, the electrical reaction and the complete recovery all point to this as the only likely diagnosis. It is interesting that the patient had repeated attacks and that her sister had suffered from a somewhat similar affliction."

Ungley[4] in 1933 reported a mother and 2 daughters with an essentially similar syndrome, emphasizing the additional clinical feature of the association of pregnancy or the puerperium with the onset of episodes of neurologic deficit.

The paucity of reports on clinical studies of this syndrome stands in contrast to the numerous studies of the neurologic complications following injection of sera and vaccines. Severe pain, wasting, and weakness due to radiculitis, particularly involving the fifth and sixth cervical nerve roots, brachial neuritis, and isolated peripheral nerve palsies, are characteristic of this condition. The brachial neuritis and mononeuritis multiplex following the administration of sera are, in their clinical features, essentially similar to those seen in the cases described in this paper. They vary in the absence of familial incidence and association with pregnancy. Parsonage and Turner[5] feel that neuralgic amyotrophy and brachial neuritis following injection of serum are essentially similar. They have described neuralgic amyotrophy as a syndrome consisting of severe pain across the shoulder and upper arm, followed by atrophic paralysis of muscles around the shoulder girdle, due primarily to involvement of nerve roots, plexus, and peripheral nerves. In most cases, this illness was not precipitated by the administration of sera or vaccines, but, in a high proportion of cases, infection, operation, or trauma appears to act as a precipitating factor. Their case material consisted largely of military personnel, and family history was not emphasized. The etiology of this condition is unknown. The clinical similarity between cases of heredofamilial neuritis, neuralgic amyotrophy, and serum neuritis will be evident.

CASE HISTORIES

The G. Family

Case 1.—*D.G. An 11-year-old girl who, at the age of 5, suffered an episode of bilateral brachial neuritis and right lumbosacral neuritis. At the age of 11, she had brachial neuritis on the right side.*

The patient was born at term after a forty-eight-hour labor and weighed 5.6 lb. She had the umbilical cord around her neck and required oxygen. She was noticed to have 2 cavernous hemangiomas 0.5 x 0.5 cm. in diameter over the dorsal aspect of the right elbow. At the age of 5 months, radon and gold seeds were implanted, following which the cavernous character of the hemangiomas receded progressively.

It had been noted since birth that her face was asymmetric, the right half of the face being smaller than the left. She turned at 7 months, sat at 1 year, walked at 19 months, and spoke well at 1½ years.

At the age of 5, she had a temperature of 104° F. followed a week later by severe headache, pain in the right scapular region and right arm, and progressive weakness of the right arm. A week later, pain developed in the left arm, followed by weakness of the abductors of the arm. The weakness progressed distally, and bilateral wrist drop developed. Her arms hung limply by her sides and were described by her mother as "dead." The pain was somewhat relieved by placing her arms in slings. She then had some pain in the right leg lasting only two or three days. During this time, she did not want to walk. Her mother noticed that her hands were hot and moist and that the weakness was followed by severe wasting of shoulder and arm muscles. Her hands were held in a claw position, and she had difficulty in opening them. After six weeks, she started to improve. Hand grip strength first returned and then she was able to flex the elbow. She was examined

at another hospital where a diffuse weakness with no segmental distribution was noticed in the arms and shoulder girdle. Sensory changes were absent, and the reflexes were diminished in the upper extremities. She received active physiotherapy and was then able to abduct both the arms. Her bilateral wrist drop was the last to recover. The entire illness lasted four months.

In September 1960, at the age of 11, she had episodes of pain in the right elbow. One week later, severe pain developed in the right scapular region, radiating into the shoulder and arm. The pain then progressed to involve the hand, and at this time she had paresthesias in her fingertips and particularly in the middle finger on that side. On two occasions, she complained of pain in her left arm and shoulder, and she had intermittent bifrontal headache. Two weeks after the onset of this episode, she had paresthesias over the radial border of her right forearm and hand, including the middle finger. Her right arm was diffusely weak, and she tended to lift it with her left hand. The arm was very tender, and she refused to let anyone touch it. She cried often, and disturbances of her sleep rhythm and slight behavior disturbances developed.

She was admitted to the Montreal Neurological Institute on November 26, 1960. On examination, she was found to be extremely small, weighing 41 lb.; her height was 47.5 in. She had closely set eyes with marked epicanthic folds and an asymmetric face, the right face being markedly smaller than the left (Fig. 1). The right arm and hand were smaller and shorter than the left, and the right chest was smaller than the left. The legs were equal in size. Over the lateral aspect of the right elbow, 2 circular scars 1.5 cm. in diameter were seen. General physical examination revealed no other abnormality, and she appeared to be of average intelligence. Neurologic examination revealed slight weakness of the right biceps, weakness of dorsiflexors of the right wrist, and weakness of grip. Weakness of opposition of the thumb and some atrophy of the first dorsal interosseus were noted. The right biceps and radial reflexes were slightly diminished as compared with the left; reflexes in the legs were equal and active. Abdominal reflexes were present, and plantar responses were flexor. Hyperesthesia to pinprick was found over the radial border of the right forearm and over all fingers. Perspiration over the right hand was excessive, and the palm had a mottled appearance.

Urine was normal; porphobilinogen was not detected. Hemoglobin was 15.3 gm.; hematocrit, 45%; sedimentation rate, 23 mm. in one hour; white blood count, 10,200. Examination of the cerebrospinal fluid revealed clear fluid under normal pressure and no cells. Cerebrospinal fluid protein was 15 mg. per cent; Lange colloidal gold curve and cerebrospinal fluid serology were normal. Radiologic examination of the skull revealed that the right anterior fossa was smaller than the left, but otherwise no definite asymmetry of size of either cerebral hemisphere was demonstrated. Roentgenograms of the legs showed no evidence of asymmetry of femora and tibiae. Humeri were symmetric, and the hands showed a mild degree of osteoporosis. The cervical spine was normal radiologically, and a venogram of the right arm revealed a normal venous pattern of the right forearm, arm, and axillary region.

Fig. 1. *(Case 1)* Physiognomy is unusual and face asymmetric.

During her stay in hospital, she was afebrile. She received physiotherapy, and progressive improvement which had started before her admission to hospital continued. The pain, sensory changes, and motor and reflex abnormalities gradually disappeared, and normal strength returned. When she was examined in 1961, reflexes in her arms were equal. No evidence of weakness or wasting and no sensory changes could be found.

Case 2—R.G. *A 15-year-old schoolboy, brother of D.G., had right-sided brachial neuritis at the age of 2½ following measles. He again had brachial neuritis at the age of 10, with some minimal left-sided involvement.*

The patient was born after an eight months' pregnancy and a fifty-two-hour labor. At birth, he weighed 5.25 lb. and showed marked cyanosis. He had a congenital cleft of the hard and soft palates, and, after the first month of life, the right half of his face was noted to be fuller than

the left; at the same time, inversion of the right foot was noted. At the age of 2½, after having measles, he had pain in his right elbow followed by diffuse weakness of his right arm and wasting of his right shoulder. He was unable to abduct the arm which hung by his side, and he cried when the arm was handled. He recovered strength in this arm in two months, and the muscle bulk gradually returned to normal. Examination one month after the onset of this illness revealed that he was very small for his age and had multiple congenital anomalies including epicanthic folds, deeply set eyes, and a cleft palate. The right face was noted to be larger than the left, and the right palpebral fissure was narrower than the left. The right shoulder was lower than the left, and the right arm was weak. He had some difficulty in abducting his arm and tended to use the left instead of the right arm. Reflex changes were not noticed. Abdominal reflexes were present and plantar responses were flexor. He had a palatoplasty at 3½ years of age.

At the age of 10 years, he had very severe pain in his right shoulder. This was followed by weakness of abductors of the arm, extending distally to involve flexors and extensors of the elbow, and, finally, a right wrist drop. At that time, he had paresthesias in his hand, which was noted to be swollen and to perspire excessively. The paresthesias involved the whole lower half of the forearm. Complete paralysis of his right arm developed and lasted one and one-half months. He received a course of physiotherapy and improved over a period of five or six months.

On some occasions, he also had pain in his left scapula and left shoulder. During this episode of weakness, some wasting of the right shoulder and arm developed; this also gradually improved.

In January 1961, at the age of 15, he was admitted to the Royal Victoria Hospital for investigation of his small stature. His intelligence was average, and he had a good school record. He weighed 71 lb. and his height was 4 ft., 5.50 in. (Fig. 2). Crown to pubis height was 26.75 in.; pubis to heel, 26.75 in.; armspread, 52 in.; chest circumference, 26 in.; head circumference, 19.5 in.; and waist, 26 in. He had facial asymmetry, the right face being more prominent than the left. He had bilateral epicanthic folds, closely set eyes, and alternating esophoria with an overactive right superior oblique muscle. He had low placed ears, the right lower than the left, with thick and malformed pinnae. The palate showed evidence of surgical repair. Neurologic examination revealed minimal weakness of abduction of his right arm and some generalized limitation of joint movement throughout, thought to be due to ligamentary inelasticity.

Fig. 2. *(Case 2)* A 15-year-old boy with unusual physiognomy and short stature

Laboratory investigations revealed normal urine and hematologic and biochemical findings. Porphyrins were not present in the urine. Roentgenograms of the chest and skull were normal. Bone age was estimated by roentgenograms of the right wrist and ankle to be between 11 and 15 years. An electroencephalogram showed some diffuse irregularities of cortical activity suggesting diffuse cerebral dysfunction, probably rather minor in character since the slow waves that were seen were intermittent in nature. Endocrine studies revealed normal levels of follicle-stimulating hormone, 17-ketosteroids, and 17-hydroxycorticosteroids. An intravenous pyelogram revealed no abnormality. A sweat test showed decreased sweating on the left half of the face as compared to the right, particularly over the temporal region.

It was felt that, like other members of his family, he suffered from genetic dwarfism.

Case 3—*P.E.G. The 42-year-old father of the first 2 patients had bilateral brachial neuritis, right lumbosacral neuritis, and lower cranial nerve palsies at the age of 27.*

The patient was a right-handed cabinet maker, 5 ft., 1 in. tall, with close and deep-set eyes and epicanthic folds.

On December 10, 1946, at the age of 27, he had a severe headache and fever. His headache disappeared in three days, and he then had severe pain in the right scapular region which prevented him at times from sleeping. Two weeks later, the pain radiated into the arm. He then noted atrophy

of his right shoulder and a tendency for the right shoulder to droop. Weakness developed and progressed distally so that he was able to eat only with his elbow on the table. He then had complete wrist drop followed by complete flaccid paralysis of the right upper limb. At that time, pain developed in the left scapula, radiating distally into the arm, with marked weakness of the left arm. He had dysesthesias and pain in the muscles of both arms. He noted changes in his voice which became "bitonal," and he had difficulty swallowing, with a tendency to choke on fluids. Some pain in his right thigh and weakness of the right leg developed which caused him to walk with a limp.

He was admitted to the Notre Dame Hospital under the care of Dr. R. Amyot on January 29, 1947. General physical examination was within normal limits. Neurologic examination revealed paralysis of the left vocal cord, which was immobile in the external position. His left sternocleidomastoid muscle was paralyzed, and, on the right, only the sternal portion of the sternocleidomastoid was seen to contract. Both trapezii were weak and slightly atrophic, the left more than the right. His tongue deviated slightly to the left. He had weakness of the latissimus dorsi and pectoralis muscles, which was more marked on the left. The left scapula was abnormally elevated, and the lower pole was displaced externally. Deltoid muscles were weak bilaterally. He was unable to flex or extend the right elbow. He had bilateral wrist drop and was unable to extend the fingers. The right triceps and both radial reflexes were absent. The knee jerks were brisk, ankle jerks normal, and plantar responses flexor. Pinprick was diminished over the radial border of the right forearm and hand, and there was a well circumscribed area of diminished sensation to pinprick over the left wrist. Touch was diminished diffusely over the right arm. Vibration sense was intact. He had dysesthesias along the radial border of both forearms, more marked on the right. Sweating increased over both arms, particularly on the palms.

He then started to improve, and, on February 11, his speech was noted to be nearly normal. Strength returned in the proximal muscles of the arms, but he still had bilateral wrist drop, more marked on the left. Muscular pain gradually diminished. Sweat testing was carried out on February 27. It was noted that he perspired more over the right forehead and temple as compared with the left. There was some patchy loss of sweating in both arms; pilomotor reflexes were absent bilaterally over irregular areas on the radial border of the forearms; and touch and temperature sensibilities were diminished in a patchy distribution over the territory of C5 through C8 bilaterally.

Investigations included roentgenograms of the cervical spine which were normal. Sedimentation rate was 9 mm. per hour. Urine was normal. Examination of the cerebrospinal fluid on February 2, 1947, revealed 2 cells; protein of 15 mg. per cent; sugar, 65 mg. per cent; chloride, 769 mg. per cent; and negative mastic reaction, Lange colloidal gold curve, and serology. He was treated with intravenous thiamine, salicylates, and physiotherapy. He was discharged with a diagnosis of neuralgic amyotrophy. At the time of discharge, he had gross atrophy of his arm and shoulder girdle musculature bilaterally, but this improved slowly and progressively.

He noted persistence of pain in his shoulders and arms with fatigue for three or four years after the initial episode; he described the pain as gnawing and like a toothache.

Fourteen years after the initial episode, he still noted some slight weakness of the shoulders when working with his arms extended above his head, particularly when lifting weights above his head. He had numbness over the radial border of his right forearm. Neurologic examination revealed only minimal weakness of abduction of his right arm, of dorsiflexion of his right wrist, and of finger extension. He had slight residual atrophy of his right deltoid and supraspinati as compared with the left. Reflexes were diminished in his arms but normal in his legs. He had an area of hypesthesia to pinscratch over the radial border of his right forearm, including his thumb. He had no recurrence of neuritis in the fourteen years following this episode.

Case 4—*M.G. A 32-year-old brother of the third patient and uncle of the first 2 patients suffered episodes of right-sided brachial neuritis at the ages of 5 and 32 years.*

The patient was a short (5 ft., 2 in.) muscular man showing the physiognomy characteristic of some members of his family—close and deep-set eyes and epicanthic folds.

At the age of 5 years, he had acute pain in his right shoulder and the scapular region, followed by weakness of his right arm, which hung lifelessly by his side and had to be worn in a sling. His strength returned gradually over some months. He later wrote and ate with his right hand but did heavy work with his left arm.

At the age of 32, he noted severe pain over the lateral border of his right arm. He then had weakness, particularly in abducting his right arm; this lasted some months. No subjective sensory changes were found at the time. He also noted wasting of his right deltoid, which also improved but did not return to normal.

On examination in 1961, when he was 37, neurologic findings were slight relative atrophy of his right deltoid, slight weakness of abduction of his right arm, and some weakness of his right supraspinati muscles. The right shoulder was lower than the left, and the scapula appeared slightly winged. There were, in particular, no sensory and reflex changes.

These patients were from a French Canadian family who had lived in a small village on the Gaspé Coast for many generations.

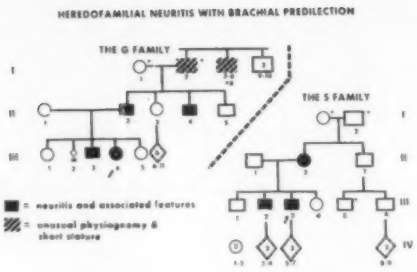
HEREDOFAMILIAL NEURITIS WITH BRACHIAL PREDILECTION
THE G FAMILY
THE S FAMILY
= neuritis and associated features
= unusual physiognomy & short stature

Fig. 3. Pedigree of G. family: III-4 is Case 1. III-3 is Case 2. II-2 is Case 3. II-4 is Case 4. Pedigree of S. family: III-3 is Case 5. III-2 is Case 6. II-2 is Case 7.

Most members of the first generation (Fig. 3) have now moved to the New England states. Of the 9 brothers of the first generation, 7 showed the small stature and physiognomy described above in members of the second and third generations. Another member of the second generation, a cousin of patients 3 and 4, had an episode of bilateral brachial neuritis following delivery; 2 of her daughters had episodes of brachial neuritis in childhood.

The unaffected siblings in the second and third generations were taller, and their appearance was dissimilar to that of the affected members. They showed no neurologic abnormality.

The S. Family

Case 5—*W.S. A 29-year-old businessman who had right-sided brachial neuritis at age 18, followed by a left radial nerve palsy at age 29.*

At 18 years of age, the patient had an acute episode of severe incapacitating pain around the right shoulder. The onset of this pain was not preceded by trauma, and he had not received any drugs or injections before onset of the symptoms. The pain persisted for ten days and subsequently gradually lessened in severity, remitting completely about one month after its onset. Limitation of movement about the right shoulder was noted while the pain was present. After remission of the pain, some wasting of the muscles around the affected shoulder with weakness of movements subserved by these muscles was observed. The weakness and wasting were not progressive and did not interfere with normal activity. The patient was afebrile throughout the episode, and therapy was limited to physical measures for alleviation of pain. In the intervening years, the patient remained in good health barring episodes of "hay fever" during the months of August and September every year.

During the last week of December 1960, the patient had an ache in the left upper arm. A week later, acute, incapacitating pain developed in the lower third of the left upper arm, mainly along its lateral border; this persisted for about ten days. Subsequently, similar pain could be reproduced by pressure over the left radial nerve in the arm. On January 12, the patient noted an area of numbness along the radial aspect of the dorsum of the left hand, and, within the next two days, wrist drop and total inability to extend the fingers of the left hand developed.

He was admitted to the Montreal Neurological Institute on January 26, 1961. He was a tall, muscular individual, with close and deep-set eyes (Fig. 4). General physical examination was normal. Neurologic examination revealed wasting and weakness of the right deltoid and right supraspinatus and infraspinatus. He had a left wrist drop (Fig. 5) and total inability to extend the fingers of the left hand at the metacarpophalangeal and interphalangeal joints. Tendon reflexes could not be elicited in either arm. Hypesthesia and hypalgesia were noted in the cutaneous distribution of the left radial nerve. The radial nerve itself was tender to palpation in the upper arm.

Laboratory investigations revealed normal urine and normal hematologic, biochemical, and serologic findings. In particular, porphyrins were not detected in the urine. Twenty-four-hour creatine excretion in the urine was 0.06 gm., and creatinine excretion was 2.1 gm. Serum protein was 7.7 gm. per cent; serum albumin, 5.27 gm. per cent; and globulin, 2.43 gm. per cent. Examination of the cerebrospinal fluid revealed 3 polymorphs per cubic millimeter; protein, 41 mg. per cent; sugar, 71 mg. per cent; chlorides, 725 mg. per cent. The Lange colloidal gold curve was normal. Electrophoretic pattern of the serum was within normal limits, and normal cerebrospinal fluid electrophoresis was also obtained. Roentgenograms of the chest, cervical spine, and skull were within normal limits, and a myelogram was also essentially normal. An electromyogram showed severe denervation of all muscles innervated by the left radial nerve. Conduction velocities along both median nerves were considered to be normal.

During his stay in hospital, there was little improvement of his weakness. When seen three months after discharge, during which time he had been receiving phsyiotherapy, power of the dorsiflexors of the left wrist and of the extensors of the fingers of the left hand had definitely improved.

Case 6.—*R.S. A 32-year old schoolteacher and brother of patient 5. He had right-sided brachial neuritis at age 9, paralysis of the vocal cords at age 16, and left brachial neuritis at age 26.*

At the age of 9, the patient suffered an episode of severe pain in his right axillary region which necessitated hospitalization. This episode was not

preceded by trauma, and the patient had not received any drugs or injections before its onset. The pain spread to involve the right arm, radiating down to the fingers, and was apparently accompanied by diffuse weakness of the right arm. The duration of the pain is not certain, but, with physiotherapy, the patient gradually recovered power in the right arm over the next six months. Thereafter, however, he always noted some weakness in the right arm.

At age 16, the patient had a sudden episode of inability to vocalize. At that time, he was examined and told that "the nerves were paralyzed in his throat." Recovery of the ability to vocalize was slow and extended over a period of six weeks, after which time there was complete recovery.

At age 26, he had an episode of pain around the left shoulder followed by difficulty in abducting the left arm above the shoulder due to weakness. Subsequently, he noted some wasting of the left shoulder, with some residual weakness when lifting the arm above the shoulder.

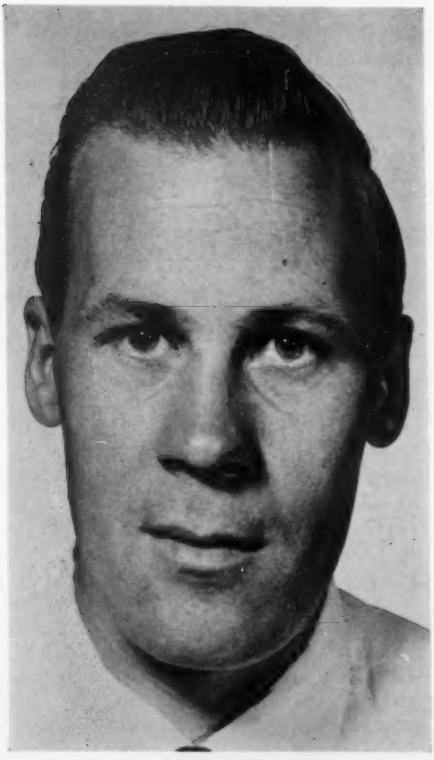

Fig. 4. (Case 5) Illustrating close-set eyes

Fig. 5. *(Case 5)* Illustrating left wrist drop

When he was examined in January 1961, a striking facial resemblance to his brother (Case 5, W.S.) was noted. In particular, he was noted to have close-set eyes. General physical examination was within normal limits. Neurologic examination revealed that the right forearm was smaller than the left and that he had some wasting of the left supraspinatus and infraspinatus muscles. Some weakness of abduction of the right thumb and external rotation of both shoulders were observed. The radial reflexes could not be elicited bilaterally, and there was a small area of hypalgesia along the distal third of the radial border of the left forearm. The peripheral nerves were not tender.

Case 7—*I.S. The 60-year-old mother of patients 5 and 6 had postpartum right-sided brachial neuritis at age 21 and median nerve paralysis on the right side at age 52.*

At the age of 21, after the delivery of her first child, the patient had pain in her right shoulder. She attributed this to a chill caused by a cold draft from an open hospital window. She was then unable to use her right arm for some two months. She was unable to do her hair, dress herself properly, or look after her child. The outstanding features of this episode in the patient's memory were the severe incapacitating pain which prevented her from sleeping and marked weakness of the right arm. The pain remitted, and strength gradually returned. There were no residual symptoms.

In 1953, at the age of 52, she had an ache anterior to the right elbow which gradually increased in intensity and was described as "terrible." The pain prevented her from sleeping and was aggravated by movement. She had considerable hyperesthesia, so that the lightest cloth touching the arm caused discomfort. Weakness of the arm was then noticed. General physical examination was normal. Neurologic examination revealed a complete loss of function of the muscles supplied by the right median nerve and sensory loss in the right median distribution. There was a suggestion of some weakness of muscles supplied by the right radial nerve. Recovery was gradual.

When she was examined in 1961, the cranial nerves were found to be normal. Reflexes in the right arm were diminished but present. There was evidence of an old right median nerve lesion with weakness and atrophy of the right thenar eminence and loss of pulp of the thumb and index finger. Loss of fine movement of the hand was noted, but the grip was good. She had no sensory loss but did have hyperesthesia of the pulp of the right thumb and index finger. No weakness, wasting, or sensory loss was found in the right upper arm and shoulder.

We were able to trace only 3 affected members in 2 generations of this family. The 2 examined members of the third generation also showed a marked resemblance to each other, particularly in their close-set eyes and round-shouldered appearance. They were of tall stature. Their facial appearance resembled affected members of the G. family, to whom they are unrelated.

DISCUSSION

In our cases, there was no evidence of involvement of the brain stem or spinal cord. The lesions appeared to be confined to the branches of the brachial plexus and, occasionally, the lower cranial nerves and the lumbar plexus. On other occasions, there was clear evidence of peripheral nerve involvement at a point considerably distal to its issue from the plexus. In the two families studied, certain differences were observed regarding localization of the lesions. The first family showed a predominance of brachial plexus involvement; the second showed, in addition, distal peripheral nerve lesions. In all patients in whom such studies were carried out, the spine was thought to be radiologically normal and, in particular, the spinal foramina were of normal size.

There was a clear preponderance of right-sided attacks of brachial neuritis (10 of 14 attacks). Involvement of the lumbosacral plexus occurred only twice and was of a mild and transitory nature; it accompanied severe, bilateral brachial neuritis. The predominance of right-sided attacks in these patients is in agreement with similar findings in cases of neuralgic amyotrophy and other neuritides where right-sided predominance is also found.

The predominant symptom at onset was pain, and this was felt to be suggestive of swelling of spinal roots or peripheral nerves. The appearance of weakness at a later stage tends to confirm this hypothesis. Electromyography confirmed the clinical evidence of denervation. No specific changes were noted on electromyography, and, where clinical recovery had taken place, no electromyographic changes could be demonstrated. The time course of recovery tends to coincide with the regeneration of nerve structures.

During the acute episodes, the muscles were tender and wasting was very marked, especially in shoulder girdle muscles.

Cranial nerves were involved in 2 patients. It is of interest that, as in Taylor's patients, the lower cranial nerves were the ones involved. Sympathetic dysfunction was demonstrated in 3 of 4 patients in the first family; in patient 3, the sympathetic changes have not regressed, nor has sympathetic function fully recovered in patient 2.

The episodes appear to be self-limiting, and recovery of function is usually good. Only once was mildly persistent pain encountered. Residual wasting was sometimes seen in the shoulder girdle muscles, and mild weakness was sometimes found. Persistent sensory changes were minimal. The sequelae of the acute episodes were never incapacitating.

Among our patients were 2 women of childbearing age who had attacks after delivery. This is again in keeping with the findings of Ungley and Taylor. The mechanism by which pregnancy or the puerperium precipitates attacks of this nature remains uncertain. Other precipitating factors in our cases included measles and a probable viral infection (Case 3).

Patient 5 (W.S.) was the only one who showed evidence of an allergic diathesis (hay fever). This evidence in itself may not be of significance. However, the similarity of this syndrome with serum neuritis suggests the possibility of a hyperergic phenomenon in the pathogenesis. The genetically determined susceptibility of peripheral nerve to this form of pathologic reaction constitutes the outstanding feature of this condition.

Genetically, the association of dwarfism and peculiar physiognomy with neuritis of brachial predilection in the G. family is of interest. The factors appear to be linked. The association of facial asymmetry and of other congenital abnormalities is also of interest. In the S. family,

the tendency to episodes of neuritis is associated with facial appearance that was strangely similar to affected members of the unrelated G. family. The pedigrees suggest that the mode of inheritance in these families is due to an autosomal dominant gene with high penetrance.[6]

The association of heredofamilial neuritis with other genetically determined external features has also been observed by Castaigne[7] in a family which he has studied.

Accurate diagnosis of this condition is important because, while it is both severe and incapacitating in its acute phase, it carries a favorable prognosis. The susceptibility of other members of these familes to a similar affliction and of the subjects to repeated episodes, particularly at certain times such as during pregnancy, must be recognized.

The early onset in 4 out of 7 cases—as early as 2½ years of age—raises the problem of accurate diagnosis of an episode of severe pain and weakness of an extremity in a small child. When this occurs after an exanthem, the misinterpretation of the signs and diagnosis of postexanthematous encephalomyelitis must be avoided. Poliomyelitis may be excluded by the absence of cells or increase in protein in the cerebrospinal fluid. In the adult, herniations of the intervertebral disk and infiltrative and other lesions of the roots in the cervical and lumbar regions must be considered. Infiltrative lesions of the brachial and lumbar plexus or of the peripheral nerve, neurologic manifestations of collagen diseases (polyarteritis nodosa, lupus erythematosus, and so on), porphyria, and diabetes mellitus have equally to be considered. This form of neuritis also must be differentiated from traumatic injury of nerve roots, plexus, or peripheral nerve.

Comparison of the syndromes described as serum neuritis, neuralgic amyotrophy, and heredofamilial neuritis with brachial predilection suggests that peripheral nerves respond in a similar manner to a variety of pathologic factors: nonspecific stress, systemic infection, injection of sera and vaccines, genetic susceptibility, and others as yet undetermined. In this study, we have stressed the heredofamilial susceptibility to such pathologic reactions. Elucidation of the nature of this pathologic process awaits pathologic and immunologic study.

SUMMARY

1. Publications describing members of three families affected with recurring episodes of brachial neuritis or mononeuritis multiplex with brachial predilection are briefly reviewed.

2. A total of 14 similar episodes in 7 patients, members of 2 unrelated families, are described.

3. The attacks are characterized by incapacitating pain, weakness, wasting, reflex changes, and sensory loss in the distribution of the brachial plexus and, rarely, lumbosacral plexus, lower cranial nerves, or peripheral nerves.

4. Involvement of the lumbosacral plexus was slight and occurred only with severe bilateral brachial neuritis. There was a strong predilection for involvement of the right upper limb. The cervical sympathetic was sometimes involved.

5. The course was self-limiting, and recovery of useful function was the rule in our cases.

6. In one family, the tendency to neuritis seemed genetically linked to dwarfism and a peculiar physiognomy; 2 of these patients showed in addition a marked facial asymmetry. In the other family, this tendency was associated with a facial appearance strikingly similar to that of the first family.

7. Transmission of the defect by an autosomal dominant gene as concluded by Taylor is confirmed.

8. The clinical similarity between cases of heredofamilial neuritis with brachial predilection, serum neuritis, and neuralgic amyotrophy is stressed, and the pathogenesis is discussed.

The authors wish to thank Dr. Prakash N. Tandon for referring Case 1, Dr. Roma Amyot for permission to consult his notes on Case 3, and Dr. F. L. McNaughton for reviewing the manuscript.

REFERENCES

1. Taylor, R. A.: Heredofamilial mononeuritis multiplex with brachial predilection. Brain 83:113, 1960.
2. Dreschfeld, J.: On some of the rarer forms of muscular atrophies. Brain 9:178, 1887.
3. Ross, J., and Bury, J. S.: On Peripheral Neuritis. London, 1893.
4. Ungley, C. C.: Quoted by Davies, D. M.: Recurrent peripheral-nerve palsies in a family. Lancet 2: 266, 1954.
5. Parsonage, M. J., and Turner, J. W. A.: Neuralgic amyotrophy. The shoulder-girdle syndrome. Lancet 1:973, 1948.
6. Metrakos, J.: Personal communication.
7. Castaigne, P.: Personal communication.

Neurologic complications of Sjögren's syndrome

Wayne Attwood, M.D., and Charles M. Poser, M.D.

In 1933, Henrik Sjögren[1] described a syndrome consisting of dryness of the mucous membranes of the eyes and parotid glandular enlargement which occurred principally in postmenopausal women. Cardinal symptoms of the disease are keratoconjunctivitis sicca, rhinitis sicca, pharyngitis sicca, xerostomia, swelling of the parotid glands, and, often, chronic rheumatoid arthritis. Other frequently associated observations are dental caries, elevated erythrocyte sedimentation rate, achylia gastrica diminished perspiration, dryness of the vulva and vagina, altered glucose tolerance curve, hypochromic anemia, raised total plasma proteins (especially the gamma globulin fraction), and alopecia.[2,3]

Because the eye involvement has been so prominent, Sjögren's syndrome was largely considered an ophthalmologic disease in the past, and it is usually ophthalmologists who first call attention to the disease. More recently, increasing evidence of its probable systemic nature has appeared in the literature. The following case, in which the neurologic observations were outstanding in the clinical picture, is reported to emphasize this point.

CASE REPORT

A.C.T., a 50-year-old white woman, was admitted to the University of Kansas Medical Center for the first time on July 9, 1958, with the chief complaint of "burning and stinging of the eyes and blurring of vision" which had been present for three months. During the previous ten years, the patient had had approximately 10 episodes of painful swelling of the parotid glands, which would last about a week and then disappear. These episodes were usually accompanied by high fever, nausea, and purulent drainage from the parotid glands. She had not noted associated eye symptoms with the parotid swellings, but she had had intermittent injection and burning of her eyes for several years. In 1953, the patient suddenly had flaccid paralysis of the right side of her face which lasted four to five weeks and gradually improved. This was not associated with any swelling of the parotid gland on the involved side. In 1954, ptosis of the right eyelid and diplopia suddenly developed, lasting approximately six weeks and gradually improving. At that time, she complained of extreme weakness and noted tingling sensations of both hands and feet which persisted to the time of admission in 1958. Slight slurring of speech and hypesthesia over the right malar eminence also developed then and persisted. She was examined at another hospital in 1954 and was told that her skull films, electroencephalogram, and lumbar puncture findings were all normal.

Since the onset of her episodes of parotid swelling, the patient had noted a gradual decrease in salivary secretion, and for five years she had been unable to swallow bread or other dry foods without moistening her mouth with water. She stated that, for several years, whenever she cried, there was no tear flow. She attributed the burning and stinging of her eyes to their dryness. The patient recalled that as a child she would perspire quite freely, but during the past few years she rarely perspired, even on the hottest days. The patient denied ever having had painful or swollen joints except for slight pain and weakness in the left hip, which were residual from an injury suffered in a fall four years before admission. The diplopia never recurred, and the patient denied having headaches, hearing loss, vertigo, weakness or tremors of her extremities, or bladder

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or bowel disturbances. She continued to have regular menstrual periods.

The patient had had smallpox at the age of 7 years. The family history was significant only in that 1 living brother had Parkinson's disease.

On physical examination, the following were noted: blood pressure, 130/80; pulse, 90 and regular; respirations, 18; temperature, 99.0° F.; height, 5 ft., 3 in.; weight, 129.5 lb. The patient was well developed and well nourished but appeared at least ten years older than her stated age of 50 years. There was a noticeable slurring of her speech. The eyes showed periorbital redness, no edema, bilateral ptosis, chronic conjunctivitis, and filamentary keratitis. The pupils were unequal and irregular and reacted sluggishly to light and accommodation. The fundi appeared normal. There was marked dryness of the oral mucosa. The parotid and lacrimal glands were not enlarged. She had moderate peripheral right facial weakness; the uvula moved to the left, and the tongue, which was noticeably atrophied on the right, deviated to the right on protrusion. The gait was somewhat wide-based, with slight ataxia on turning. Coordination on either foot was poor. There was slight dysdiadochokinesia, and, except for sluggish patellar reflexes, which were equal bilaterally with reinforcement, the patient was areflexic. Her plantar responses were flexor; she had diminished vibratory sense of both lower extremities. Position, tactile, and pain sensations were intact throughout. There was no evidence of joint swelling or deformities, and the remainder of the physical examination was essentially negative.

The laboratory findings are summarized in the table. Cobalt-60-tagged B_{12} uptake was 12% of the orally administered dose in twenty-four hours. Electrocardiogram and electroencephalogram were considered normal. Chest roentgenograms were normal. Skull films showed local hyperostosis of the frontal bone. Roentgenograms of both hands showed moderate periarticular demineralization of bone but no specific changes. Bone marrow was interpreted as normal with moderate cellularity. Schirmer's test showed 2 mm. of wetting on the right and 2 mm. on the left in five minutes (normal, 12 mm.).

The patient was slightly febrile on admission and had an intermittent slight fever throughout her hospital stay. She remained relatively asymptomatic except for the presenting complaints. After chewing on a piece of paraffin for ten minutes, the patient was unable to generate enough saliva to analyze for salivary electrolytes. In order to determine whether the patient could perspire, a saturated solution of cobalt chloride was painted on her back, with the blue color forming. After she was put under 2,000 watts of light for thirty minutes, the color gradually began to turn pink. The test was completed in sixty minutes, showing that the patient could perspire but only very slowly and in small quantities. The patient was discharged from the hospital after the completion of various diagnostic procedures. The medication prescribed was triamcinolone in a dosage of 2 mg. twice a day.

The patient was readmitted for reevaluation in May 1960. She stated that she had improved considerably in that her strength was better in the lower extremities, her eyesight had improved, and she no longer experienced numbness of the legs and feet and burning sensations of the palms of her hands. She had had no recurrence of swelling of the parotid gland. She had lost no time from her work.

The general and neurologic examinations revealed exactly the same findings as during her first admission. The results of various laboratory procedures are summarized in the table. Thus, in spite of remarkable subjective improvement, no objective changes could be detected by physical or laboratory examinations. At least, no evidence of progression of the disease was found.

DISCUSSION

The etiology of Sjögren's syndrome has remained totally obscure since its original description. The similarity of the eye symptoms to those seen with vitamin A deficiency led to early speculation that this might indeed be a deficiency state. Franceschetti[4] pointed out the similarity among the Plummer-Vinson syndrome, Sjögren's syndrome, and ariboflavinosis. The high incidence of the syndrome in postmenopausal women has suggested an endocrine factor in its pathogenesis.[5] In 1951, Sjögren[6] wrote that "today it seems to be the most correct to count with double etiology,

infection and endocrine disturbance. However, the endocrine component nowadays seems to be still more important than has been supposed earlier." In this regard, he emphasized that the patients tend to look older than their stated age,[7] which was apparent in this case.

Gruber[8] has reported a case of Sjögren's syndrome in a 50-year-old woman with accompanying enlargement of the thyroid gland similar to that seen in Hashimoto's type of chronic thyroiditis. This condition is also generally observed in women past 40 and may be associated with rheumatoid arthritis. In it, the thyroid gland shows an extensive lymphoid infiltration and atrophy of the glandular parenchyma and fibrosis. This histologic pattern is like that noted in the lacrimal or salivary glands in Sjögren's syndrome. The frequent reports of elevated serum gamma globulin levels in cases of Sjögren's syndrome led Jones[9] to postulate that autoantibodies in the serum were responsible for the glandular destruction. In one patient, circulating precipitating antibodies to extracts of lacrimal and salivary glands of cadavers were observed. He thought that the mechanism may be similar to that recently described in Hashimoto's disease, in which the presence of autoantibodies to thyroglobulin has been detected.[10]

Gordon and Shanbrom,[11] after demonstrat-

LABORATORY EXAMINATIONS

	July 1958	*May 1960*
Blood		
Hemoglobin (gm. per 100 cc.)	11.0 12.8	14.4
White cells (per cu. mm.)	4,800 5,470	5,800
Hematocrit (%)	36.5	47
Platelets (per cu. mm.)	175,000	164,000
VDRL	Negative	Negative
Urea nitrogen (mg. per 100 cc.)*	21, 27, 22	27, 25
Creatinine (mg. per 100 cc.)*	2.3, 1.9	1.7
Fasting sugar (mg. per 100 cc.)	76	63
Cholesterol (mg. per 100 cc.)	160	165
Cholesterol esters (%)	57	67
Carbon dioxide (mEq. per liter)	16.8	21.2
Sodium (mEq. per liter)	136	139
Potassium (mEq. per liter)	4.4	4.4
Chloride (mEq. per liter)	106	105
Calcium (mEq. per liter)	4.5	4.6
Phosphorus (mEq. per liter)	2.3	2.5
Albumin (gm. per 100 cc.)*	2.96, 2.54	2.96
Globulin (gm. per 100 cc.)*	6.92, 7.34	6.45
Glucose tolerance (mg. per 100 cc.)	80, 198, 110, 70, 32	
Wintrobe erythrocyte sedimentation rate (mm. per hour)	24	22
Direct bilirubin (mg. per 100 cc.)	Negative	0.2
Total bilirubin (mg. per 100 cc.)	0.2	0.3
Alkaline phosphatase (millimol units)	1.7	1.3
Thymol turbidity (units)	28	23
Bromsulphalein retention		3%
Cephalin-cholesterol	Negative	Negative
C-reactive protein	2+	
Antistreptolysin-O titer (units)	12	
Mucoproteins (normal, less than 300)	406	
Weltman (right shift)	8	

LABORATORY EXAMINATIONS (continued)

	July 1958	*May 1960*
Urine		
Specific gravity*	1.006, 1.004	1.003
Albumin	Heavy trace	Faint trace
Pus cells (per high-power field)	6–8	Occasional
Red blood cells (per high-power field)	1–2	None
24-hour sodium excretion (mEq. per total volume of 3,800 cc.)	105	73
24-hour potassium (mEq.)	52	47
24-hour chloride (mEq.)	197	49
Bence Jones protein	Negative	
Cerebrospinal fluid		
White cells (per cu. mm.)*	6, 14	2
Red blood cells (per cu. mm.)*	7, 101	0
Protein (mg. per 100 cc.)*	39, 63, 52	28
Colloidal gold*	5552210000 5555532100 5555531100	5553211000
Serology	Negative	Negative
Miscellaneous		
Lupus erythematosus cell preparation	Negative	Negative
Sweat test (mEq. Na per liter of sweat)	31	12, 17
Gastric analysis		
Without Histalog (degrees)	Free: 22, 40, 42 Total: 68, 70, 64	
With Histalog (degrees)	Free: 88, 128, 130, 134 Total: 96, 134, 140, 138	
Sia test	Positive	
Cryoglobulins	Negative	Negative
Macroglobulins	Negative	Negative
Serum electrophoresis		
Albumin (normal, 56%)*	38, 20	16
Globulins		
α_1 (normal, 4%)*	4, 4	4
α_2 (normal, 9%)*	15, 9	12
β (normal, 14%)*	16, 14	9
γ (normal, 17%)*	27, 53	59

*Multiple determinations

ing diminished secretions of the lacrimal and salivary glands, bronchial mucosa, stomach, and pancreas in a patient with Sjögren's syndrome, suggested that Sjögren's syndrome may represent an alteration in the physiology of the exocrine glands of the body and postulated a relationship to cystic fibrosis of the pancreas. While the patient in the case herein reported demonstrated a perceptible diminution in the ability to sweat, the normal concentration of sodium in the sweat would strongly rule against any relationship to cystic fibrosis of the pancreas. The observation of abnormally high concentrations of electrolytes in the sweat has come to be recognized as characteristic of this disorder.[12]

The relationship of Sjögren's syndrome to rheumatoid arthritis and the collagen diseases must be considered. Holm,[13] after an extensive review of Sjögren's syndrome, stated that "the conception of keratoconjunctivitis sicca as a disease sui generis is fundamentally incorrect," and he concluded that there is strong reason to suggest that chronic rheumatoid arthritis is important as an etiologic factor in the appearance of Sjögren's syndrome. Sjögren retorted that "my opinion is the one generally adopted that arthritis belongs to the syndrome, but . . . there is no causal connection between the articular symptoms and the other symptoms. All symptoms are the expression of a common ground disease."[6]

The increasing frequency with which Sjögren's syndrome is being associated with other of the collagen diseases lends further support to its inclusion in this group. In a case of Sjögren's syndrome reported by Cardell and Gurling,[14] observations made at autopsy included "vascular lesions typical of polyarteritis nodosa . . . in both kidneys, both adrenals, and the liver, spleen, pancreas, small and large intestines, and myocardium." In another case, histologic examination of the lacrimal and salivary glands revealed a well-developed obliterative endarteritis.[14] Littler[15] published a case of Sjögren's syndrome combined with Felty's syndrome, rheumatoid arthritis, and rheumatic heart disease. Ramage and Kinnear[16] have recently reported Sjögren's syndrome associated with polyarteritis nodosa, disseminated lupus erythematosus, and scleroderma. Sokoloff and Bunim,[17] in a discussion of the vascular lesions of rheumatoid arthritis, mentioned one patient with Sjögren's syndrome "found to have, on biopsy of the sartorius muscle, arterial changes typical of polyarteritis nodosa." The laboratory observations which have come to be recognized as typical of the collagen diseases—elevated erythrocyte sedimenation rate, diminished serum albumin, elevated serum globulins, abnormal flocculation tests, and abnormal serum electrophoretic patterns—are frequently seen in Sjögren's syndrome.

The neurologic changes in the present case consist of multiple cranial nerve palsies and peripheral neuropathy. Reports of neurologic abnormalities in cases of Sjögren's syndrome have been scanty. In his earlier writings,[18] Sjögren mentioned one patient (Case 9) with bilateral seventh nerve neuritis. He also had noted occasional transitory sensory changes of the cornea and skin of the face, but he did not feel that this represented trigeminal involvement. Weber[19] mentioned having examined a patient with Sjögren's syndrome in whom the pupils were unequal and inactive, the left pupil was irregular, and there was bilateral ptosis. Examination of the nervous system was otherwise negative. In an autopsied case of Sjögren's syndrome, Szanto, Farkas, and Gyulai[20] noted perineural and intraneural round cell infiltrations similar to those found in the vascular system, but this was not associated with any clinical neurologic changes.

In the present case, the cerebrospinal fluid examination showed alterations consisting of a slight elevation of protein and white cells and an abnormal colloidal gold curve. Sundelin[21] examined the cerebrospinal fluid in 141 cases of rheumatoid arthritis and found a total of 66 cases (46.8%) in which the spinal fluids were altered in some way, that is, an elevated protein content, an abnormal colloidal gold curve, or an increased cell count. There was no correlation between the abnormalities of the spinal fluid and the severity or length of the arthritic disease process. Ludwig, Short, and Bauer[22] noted similar changes in the cerebrospinal fluid in 25 of a series of 101 cases of rheumatoid arthritis. In a study of the electrophoretic patterns of concentrated cerebrospinal fluid, Kabat, Landow, and Moore[23] observed that cerebrospinal fluid proteins showed a pattern similar to that of plasma proteins and concluded that alterations of the serum proteins are reflected in the cerebrospinal fluid. This seems to be the most logical explanation of the abnormalities noted in the spinal fluid in this case, the abnormalities being secondary to the basic disease process rather than indicative of any primary or unrelated disease of the central nervous system.

Workers in rheumatology have become increasingly aware in recent years of polyarteritic features of rheumatoid arthritis, particularly since steroid therapy has become so widely used in this disorder. Cruickshank,[24] in a series of 72 cases of rheumatoid arthritis which came to autopsy, noted evidence of arteritis in 18 cases. Lesions were seen principally in

the heart, peripheral nerves, and muscles. A review of 52 cases of rheumatoid arthritis studied at autopsy by Kemper, Baggenstoss, and Slocumb[25] revealed evidence of arteritis in 12 cases. Whether the arteritis seen in rheumatoid arthritis is distinguishable from other types of arteritis is uncertain. Cruickshank[24] has expressed the belief that the arterial lesions in rheumatoid arthritis differ in several respects from the other types of arteritides, that is, infrequent visceral involvement, anatomic distribution, and lack of characteristic changes noted in other diseases such as aneurysms or thromboses. On the other hand, Ball[26] has described 4 patients with typical rheumatoid arthritis who, at autopsy, were noted to have polyarteritis nodosa involving most of the viscera and 1 patient with polyarteritis nodosa who at autopsy was seen to have the typical joint changes of rheumatoid arthritis independent of the arterial changes. He believed that "the available evidence suggests that the distribution, frequency, and morphology of arterial lesions in rheumatoid arthritis are variable, ranging from a mild indeterminate arteritis to classical polyarteritis nodosa."[26]

Concomitant with the increasing recognition of vascular lesions as a complication of rheumatoid arthritis has been an increase in the reporting of peripheral neuropathies in this condition. Irby, Adams, and Toone[27] wrote about 6 cases of rheumatoid arthritis with a peripheral neuritis involving the lower extremities in all cases and the upper extremities in 3. Spinal fluid examinations were normal except in 1 case in which the protein was elevated to 90 mg. per 100 cc. A section from the sciatic nerve in 1 case in which a leg later had to be amputated showed vasculitis and perivasculitis in the center of the nerve trunk. All the patients in this series had been treated with steroids in sufficiently large quantities and over long enough periods of time to produce symptoms of hypercorticalism. Hart, Golding, and MacKenzie[28] reported 10 patients with rheumatoid arthritis who had pronounced neuropathies in the course of their disease. They believed the arteritis to be the basis of the rheumatoid neuropathy since "(a.) the patients with neuropathy are mostly relatively advanced rheumatoids of long standing, and the disease is not particularly active at the time of the development of the condition; (b.) a withdrawal of steroid suppressive therapy seems more likely to be followed by a peripheral neuropathy than does a natural relapse; and (c.) high dosage suppressive steroid therapy does not improve the neuropathy as it does other features of the arthritis."[28]

It is of interest here to note that 5 of the 10 patients had never received steroids. In the series of 52 patients with rheumatoid arthritis studied by Kemper and associates,[25] 4 had clinical signs and symptoms of a severe degree of peripheral neuropathy; at autopsy, angiitis involving many of the peripheral nerves was noted. Of particular interest was Case 3, in which the patient suffered what appeared to be a cerebral infarction but at autopsy was found to have a basilar artery thrombosis with a severe inflammatory reaction involving the walls of the artery and resulting in obliteration of the lumen with infarction of the right pons. It seems possible that the cranial nerve abnormalities in our patient might be explained on a similar basis, that is, an inflammatory involvement of the basilar artery resulting in vascular insufficiency. A case (Number 6) of multiple cranial nerve palsies, similar to those described in the present case report, was reported by Sokoloff and Bunim[17] in a patient with rheumatoid arthritis of twelve years' duration. Another patient (Number 2) with rheumatoid arthritis of nine years' duration coupled with diffuse polyneuropathy was found to have left facial weakness of the central type. While corticosteroid therapy has been incriminated as the exciter of these neuropathies in rheumatoid arthritis,[29,30] observing this condition in patients who, as in the present case, have received no corticosteroids indicates that neuropathies as well as vasculitis may be considered true complications of rheumatoid arthritis.[28]

The occurrence of polyarteritic lesions with rheumatoid arthritis resulting in cranial and peripheral neuropathies is well documented. This fact is of heightened interest with regard to the present case, in which there were similar observations of multiple cranial nerve palsies plus diffuse peripheral neuropathy. That the patient in the present case also presented the typical indications of Sjögren's syndrome seems to provide strong evidence of a link between the two conditions, rheumatoid arthritis and

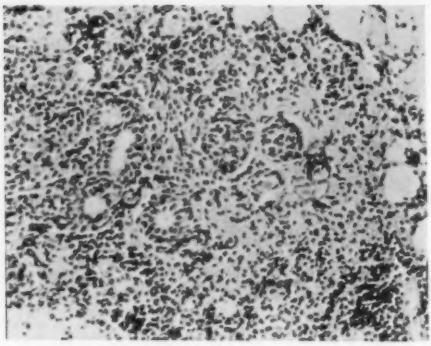

Fig. 1. Parotid gland biopsy showing 1 area of heavy round cell infiltration. Within area, 2 myoepithelial islands may be seen. × 125

Sjögren's syndrome. Sjögren's syndrome is generally accepted as a distinct clinical and pathologic entity, but the present instance makes a strong case for its inclusion in the ill-defined group of collagen diseases. Improvement of the ocular symptoms and temporary regression of the parotid swellings with steroid therapy lend support to this view.[8,31]

Pathologic observations in the affected lacrimal and salivary glands include atrophy of the glandular parenchyma with infiltrates of round cells and increased formation of fibrous tissue.[5,32] As the disease progresses, intraductal proliferation has been noted within the salivary glands of two cell elements, epithelial and myoepithelial, with the formation of myoepithelial islands.[2,33,34] The parotid gland biopsy which was obtained in this case well typifies these observations. One area of heavy round-cell infiltration is shown in Figure 1. Within the area, two myoepithelial islands may be seen (Fig. 2). Similar histologic observations have been noted in Mikulicz's syndrome, and it has been suggested that the latter is not a distinct clinical and pathologic entity but a manifestation of Sjögren's syndrome.[33,34]

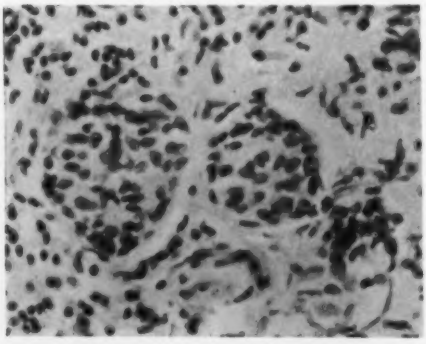

Fig. 2. Close-up of 2 myoepithelial islands shown in Figure 1. × 340

In the differential diagnosis of Sjögren's syndrome, other common causes of parotid swelling, such as mumps, infectious parotitis, salivary calculus, and parotid gland tumors generally present no difficulties. In Mikulicz's syndrome, which is probably an incomplete form of Sjögren's syndrome, xerostomia and eye symptoms are rare.[35] Heerfordt's syndrome (uveoparotitis) generally occurs in younger persons (second and third decade), xerostomia is unusual, and keratitis, mucous membrane changes, and rheumatoid arthritis are not present.[2,5,35] Vitamin A deficiency produces xerosis of the eyes and changes in the mucous membranes, but the disturbance of dark adaptation reveals the true nature of the condition.[5] The only other eye condition to be confused with keratoconjunctivitis sicca is that of keratitis neuroparalytica, but a history of trigeminal root section serves to differentiate the two.

Since the cause of Sjögren's syndrome is unknown, treatment must be symptomatic. Large doses of vitamins, thyroid extract, and estrogens have proved to be of no value, and results of therapy with pilocarpine and neostigmine have generally been unsuccessful.[4,36,37] Treatment directed toward ocular symptoms has been more successful and includes some type of eyewash or solution and electrocoagulation of the lacrimal ducts in an attempt to preserve whatever natural tears may remain.[29,35] The latter procedure should not be attempted in early or mild cases in which a remission might be expected, as a return of lacrimal secretion may lead to epiphora.[37] Systemic steroid treatment has been the most effective therapy thus far, particularly for the relief of parotid swellings.[8,14,31] However, side effects and complications of prolonged high doses have limited their usefulness.

SUMMARY

A case of Sjögren's syndrome is reported in which, in addition to the typical observations in this disease, the patient had multiple cranial nerve palsies and diffuse peripheral neuropathy. A markedly abnormal serum electrophoretic pattern was seen which was reflected in the cerebrospinal fluid.

A review of the literature reveals that the etiology of Sjögren's syndrome has been attributed to a deficiency state, to chronic infection, to an endocrine disturbance, to autoimmunization, to a generalized disease of the exocrine glands, and to rheumatoid arthritis and the collagen diseases. In view of the similarities between the neurologic changes in this case and those which are being reported with increasing frequency in rheumatoid arthritis, it is felt that Sjögren's syndrome, while still a distinct clinical and pathologic entity, is closely related to rheumatoid arthritis and most properly belongs in the collagen group of diseases.

The pathologic observations, differential diagnosis, and treatment of Sjögren's syndrome are reviewed.

The authors wish to express their appreciation for the kind help and cooperation of Drs. Joe Boley, Philip Kaul, Gene Malone, Glen Snodgrass, John Weininger, John Wheeler, and Richard Ye.

REFERENCES

1. Sjögren, H.: Zur Kenntnis der Keratoconjunctivitis sicca. Keratitis filiformis bei Hypofunktion der Tränendrüsen. Acta ophth. Supp. 2:1, 1933.
2. Ehrlich, J. C., and Greenberg, D.: Sicca syndrome; Gougerot-Sjögren disease. Arch. Int. Med. 93:731, 1954.
3. McLenachan, J.: New aspects of the aetiology of Sjögren's syndrome. Tr. Ophth. Soc. U. Kingdom 76: 413, 1956.
4. Franceschetti, A.: Le syndrome de Sjögren: Ses rapports avec le syndrome de Plummer-Vinson et l'avitaminose B_2. Confinia neurol. 4:343, 1942.
5. Gamp, A.: Sjögren's syndrome. Rheumatism 14:51, 1958.
6. Sjögren, H.: Some problems concerning keratoconjunctivitis sicca and the sicca-syndrome. Acta ophth. 29:33, 1951.
7. Sjögren, H.: Keratoconjunctivitis sicca and chronic polyarthritis. Acta med. scandinav. 130: 484, 1948.
8. Gruber, E.: Sarcoidosis of the lacrimal glands associated with Sjögren's syndrome; their relationship with Mikulicz's syndrome. Arch. Ophth. 55:42, 1956.
9. Jones, B. R.: Lacrimal and salivary precipitating antibodies in Sjögren's syndrome. Lancet 2:773, 1958.
10. Doniach, D., and Roitt, I. M.: Auto-immunity in Hashimoto's disease and its implications. J. Clin. Endocrinol. 17:1293, 1951.
11. Gordon, M. E., and Shanbrom, E.: The systemic manifestations of Sjögren's syndrome: Report of glandular function with histological, bacterial, and viral studies. Ann. Int. Med. 48:1342, 1958.
12. di Sant'agnese, P. A., Darling, R. C., Perera, G. A., and Shea, E.: Abnormal electrolyte composition of sweat in cystic fibrosis of the pancreas. Pediatrics 12: 549, 1953.
13. Holm, S.: Keratoconjunctivitis sicca and the sicca syndrome. Acta ophth. Supp. 33:1, 1949.
14. Cardell, B. S., and Gurling, K. J.: Observations on the pathology of Sjögren's syndrome. J. Path. & Bact. 68:137, 1954.
15. Littler, T. R.: The changing pattern of rheumatoid arthritis. Ann. Rheumat. Dis. 10:405, 1951.
16. Ramage, J. H., and Kinnear, W. F.: Kerato-conjunctivitis sicca and the collagen diseases. Brit. J. Ophth. 40:416, 1956.
17. Sokoloff, L., and Bunim, J. J.: Vascular lesions in rheumatoid arthritis. J. Chron. Dis. 5:668, 1957.
18. Sjögren, H.: Zur Kenntnis der Keratoconjunctivitis sicca. II. Allgemeine Symptomatologie und Ätiologie. Acta ophth. 13:1, 1935.
19. Weber, F. P.: Sjögren's syndrome, especially its non-ocular features. Brit. J. Ophth. 29:299, 1945.
20. Szanto, L., Farkas, K., and Gyulai, E.: On Sjögren's disease. Rheumatism 13:60, 1957.
21. Sundelin, F.: Investigations of the cerebrospinal fluid in cases of rheumatoid arthritis. Am. J. Med. 2: 579, 1947.
22. Ludwig, A. O., Short, C. L., and Bauer, W.: Rheumatoid arthritis as a cause of increased cerebrospinal fluid protein; study of 101 patients. New England J. Med. 228:306, 1943.
23. Kabat, E. A., Landow, H., and Moore, D. H.: Electrophoretic patterns of concentrated cerebrospinal fluid. Proc. Soc. Exper. Biol. & Med. 49:260, 1942.
24. Cruickshank, B.: The arteritis of rheumatoid arthritis. Ann. Rheumat. Dis. 13:136, 1954.
25. Kemper, J. W., Baggenstoss, A. H., and Slocumb, C. H.: The relationship of therapy with cortisone to the incidence of vascular lesions in rheumatoid arthritis. Ann. Int. Med. 46:831, 1957.
26. Ball, J.: Rheumatoid arthritis and polyarteritis nodosa. Ann. Rheumat. Dis. 13:277, 1954.
27. Irby, R., Adams, R. A., and Toone, E. C., Jr.: Peripheral neuritis associated with rheumatoid arthritis. Arthritis & Rheumatism 1:44, 1958.
28. Hart, F. D., Golding, J. R., and MacKenzie, D. H.: Neuropathy in rheumatoid disease. Ann. Rheumat. Dis. 16:471, 1957.
29. Henderson, J. W.: Keratoconjunctivitis sicca; a review with survey of 121 additional cases. Am. J. Ophth. 33:197, 1950.
30. Jones, B. R., and Stevenson, C. J.: Keratoconjunctivitis sicca due to sarcoidosis. Brit. J. Ophth. 41:153, 1957.
31. Cadman, E. F. B., and Robertson, A. J.: The treatment of Sjögren's syndrome with A.C.T.H. Brit. M. J. 2:68, 1952.
32. Ellman, P., Weber, F. P., and Goodier, T. E. W.: A contribution to the pathology of Sjögren's disease. Quart. J. Med. 20:33, 1951.
33. Morgan, W. S.: The probable systemic nature of Mikulicz's disease and its relation to Sjögren's syndrome. New England J. Med. 251:5, 1954.
34. Morgan, W. S., and Castleman, B.: A clinicopathologic study of "Mikulicz's disease." Am. J. Path. 29: 471, 1953.
35. Cadman, E. F. B.: Sjögren's syndrome. Med. Illus. 7:601, 1953.
36. Harrington, A. B., and Dewar, H. A.: A case of Sjögren's disease with scleroderma. Brit. M. J. 1:1302, 1951.
37. Thompson, M., and Eadie, S.: Kerato-conjunctivitis sicca and rheumatoid arthritis. Ann Rheumat. Dis. 15: 21, 1956.

Double collimator isotope detection for study of carotid blood flow

A preliminary report

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BLOOD FLOW STUDIES utilizing isotopes include arterial and venous samples of isotope-containing blood and measurement of time between detection in the carotid artery and the jugular bulb. Oldendorf and Crandall[1] have utilized measurement of radioactivity on the two sides of the head for qualitative differences of blood flow after injection of a radioactive isotope into a body vein. Recently, Hardesty and associates[2] have reported on measurement of blood flow in the carotid complex in the neck during surgical exposure. They have used a noncannulating electromagnetic flowmeter for this purpose.

A method for measuring blood flow in the two carotid arteries in the neck or the one carotid pre- and postoperatively has been investigated by the use of a specially designed double collimator for gamma rays. When the two detectors are placed along the carotid artery at a known distance, the arrival of a radioactive substance at each detector will give off a peak signal. A peak-to-peak signal in the known distance between the points of collimation may be used to indicate the velocity of flow.

In this preliminary report, experimental work on dogs will be analyzed; although the carotid system of vessels in the dog is different from that found in man, the possible application of the method for human experience seems reasonable and feasible.

INSTRUMENTATION

Figure 1 shows a diagram of the experimental setup. A gamma ray emitter, radioiodinated serum albumin (RISA), is injected into an extremity vein, and, after passing through the heart and lungs, part of the initial bolus travels up the carotid artery under observation. The sudden increase in activity is recorded by the two scintillation detectors, and the time interval between the two peak readings is scaled off the recorder.

The collimator is a scintillation detector divided into 2 detecting parts with a known distance between. When a single counter divided into 2 detecting portions is used, mechanical errors in detection of activity are minimal or none. For this purpose, a large detector with a sodium iodide (T1) crystal 3-in. in diameter is used with the collimation head so designed as to take the place of 2 detectors. This eliminates the use of 2 sets of electronic equipment and represents not only a saving in cost but also a greater assurance of the accuracy of the response time. Figure 2 shows the adopted design of a double lead cone collimator which focuses on 2 points 2⅝ in. apart and 4½ in. below the surface of the crystal. The collimation is affected by molding lead in such a fashion as to produce 2 annular air spaces in the form of half cones, skewed so that they come together toward the surface of the crystal.

The pulses from the photomultiplier tube associated with the NaI (T1) crystal pass through a preamplifier and are then linearly amplified before they are fed into the discrimi-

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This study was aided by the Kresge Foundation and the National Heart Institute.

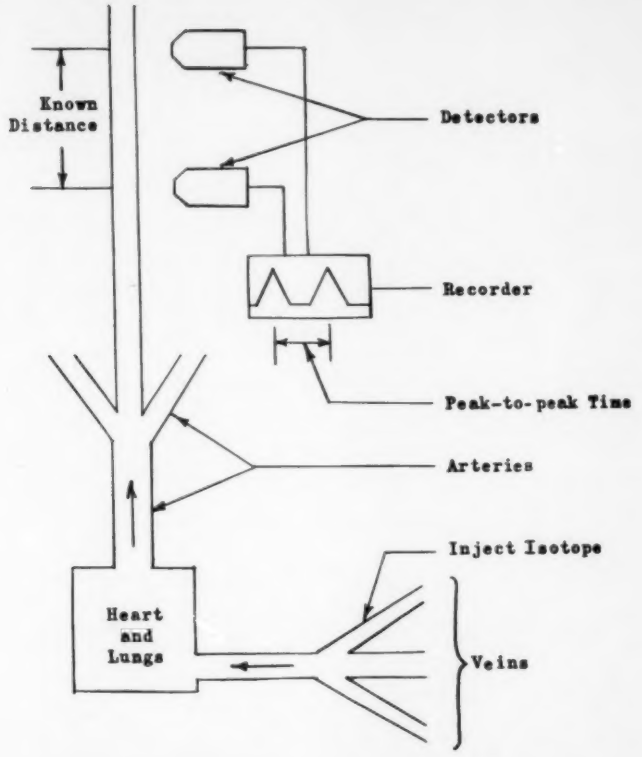

Fig. 1. Sketch of new qualitative concept of blood flow measurement

nator circuits of the spectrometer. The window width is set at 2 volts, and the selected pulses emerging from the spectrometer are amplified and recorded by means of a Brush recorder. Figure 3 shows a block diagram of the instruments used.

When the isotope passes under the first cone of the collimator, the count increases, pulses occurring at shorter time intervals, representing an increase in slope as shown in Figure 4a. As the isotope passes under the second cone, a similar curve is obtained with the exception that there is a time delay, or the time the isotope takes to travel from one point to the next (Fig. 4b). Figure 4c and d show a combination of the 2 curves in which the slopes have been added together. This is the curve obtained by plotting the cumulative counts versus time from the Brush recorder charts. The cumulative effect is the result of using one detector for both points. The anticipated double peak as shown in Figure 1 can no longer be obtained, and instead 2 other alternative forms are to be expected. As the indicator arrives at the second point of detection before the rise of the first curve is completed, the form obtained is that of 3 straight lines, with each succeeding line having a steeper slope than the previous one (Fig. 4c). The first line represents the count rate due to background. If the indicator arrives at the second point while the activity at the first point has already passed its peak and is undergoing "decay," it assumes the form shown in Figure 4d. The 2 steeper lines are joined by 1 of milder slope indicating a period of low activity. These 2 characteristic forms shall be denoted as type A and type B, respectively.

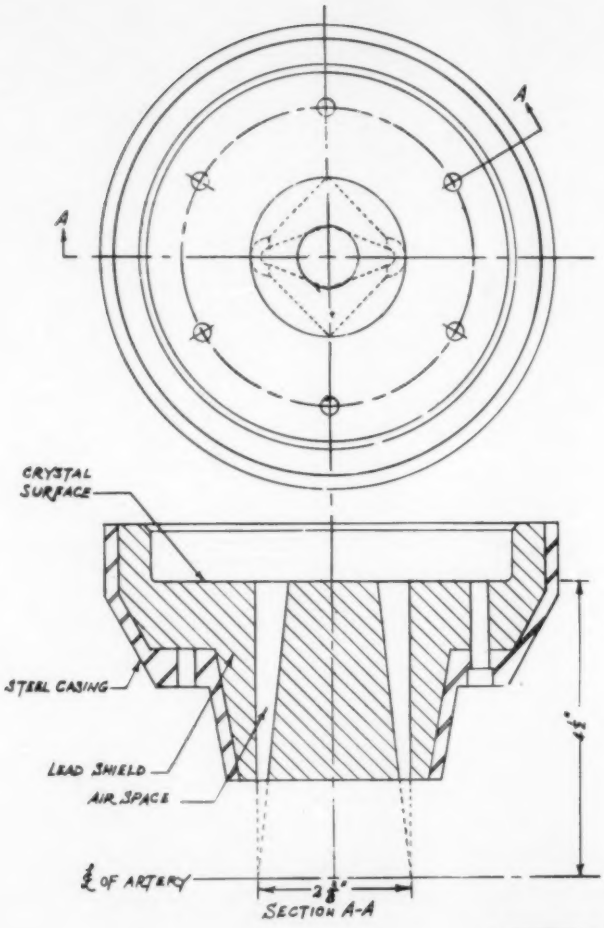

Fig. 2. Adopted [illegible] of double lead cone collimator

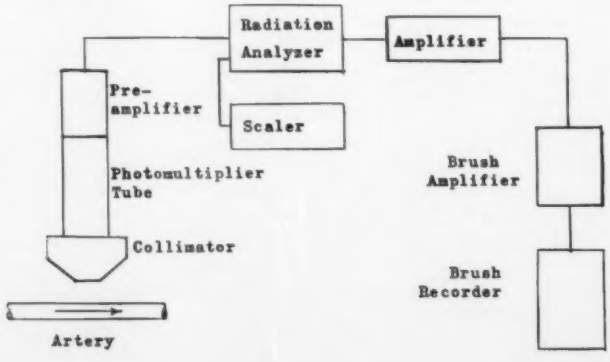

Fig. 3. Block diagram of instrumentation

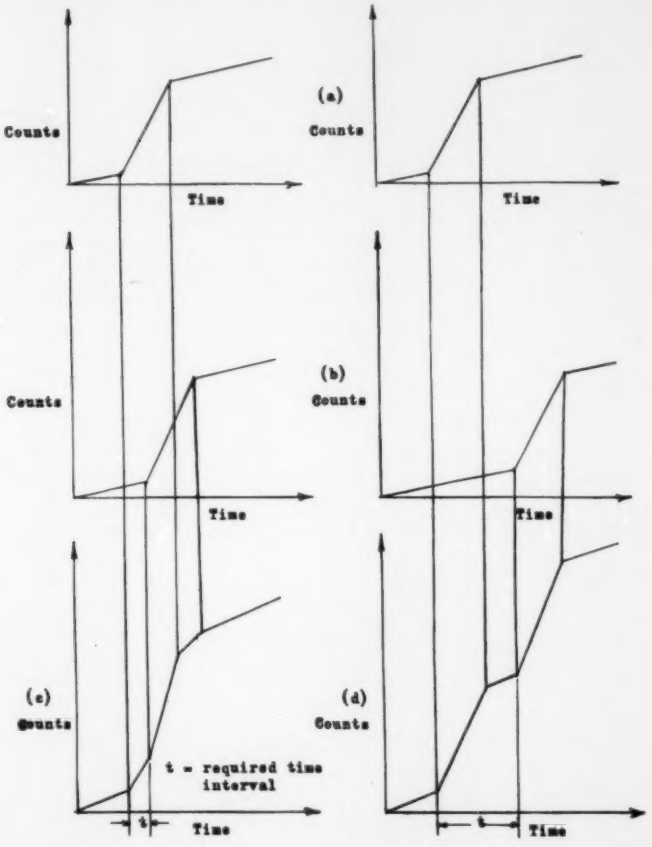

Fig. 4. Type A curve, left: Isotope arrives under second window before steep rise under first window is completed. Type B curve, right: There is a period of low activity before arrival of isotope under second window.

If the isotope is distributed in the flow according to the velocity distribution curve, it is possible for the detector to give consistently higher values of velocity. For laminar flow, the error can be as great as 100%; however, there is a large amount of suspension of blood cells being carried in the blood stream. The cells tend to form a central core in the vessel, and the isotope, carried mainly in the plasma, can be displaced toward the peripheral region. Here the velocity of flow is close to the average velocity, and the measured value is thus not expected to deviate very much from the mean flow velocity.

We have noted that the isotope appears to remain for a time in the blood stream as discrete globules, and this adds to the accuracy of the measurement by allowing for a whole series of measurements to be made within a very short time interval. Furthermore, if successively increasing doses of isotope are used, measurements may be repeated in the same experiment several times at the same sitting. The length of the stream of isotope globules determines the type of curves obtained. Type A curves are expected for long streams and type B for short ones. Use of different isotopes injected at intervals may also give valuable information on blood flow, as can be seen in Tests 22, 23, 25, and 26 listed in the table.

Test no.	Dog no.	Weight of dog (kg.)	Artery used	Measurement made over	Condition of other arteries	Isotope used — Type	Isotope used — Amount (μc.)	No. of characteristic curves obtained	Average time interval (seconds)
1	1	15.5	Right common carotid	Unexposed artery	Left common carotid and both vertebrals patent	I^{131}	100	1	0.425
2	2	15	Right common carotid	3/16" internal diameter plastic siliconized cannula	Left common carotid and both vertebrals patent	I^{131}	60	2	0.580
3	3	23.5	Right common carotid	Cannula	Left common carotid and both vertebrals patent	I^{131}	36	2	0.195
4	3	23.5	Right common carotid	Cannula	Left common carotid and both vertebrals patent	I^{131}	123	3	0.490
5	1	16.5	Left common carotid	—	Right common carotid and both vertebrals patent	I^{131}	55	—	—
6	1	16.5	Left common carotid	—	Right common carotid and both vertebrals patent	I^{131}	165	—	—
7	4	24	Left common carotid	Cannula	Right common carotid and both vertebrals patent	I^{131}	60	2	0.653
8	4	24	Left common carotid	Cannula	Right common carotid and both vertebrals patent	I^{131}	120	2	0.120
9	4	24	Left common carotid	Cannula	Right common carotid and both vertebrals patent	I^{131}	200	4	0.149
10	5	15	Left common carotid	Cannula	Right common carotid ligated; both vertebrals patent	I^{131}	45	3	0.347
11	5	15	Left common carotid	Cannula	Right common carotid and both vertebrals ligated	I^{131}	90	2	0.145
12	6	11.5	Right common carotid	Cannula	Left common carotid and both vertebrals patent	I^{131}	70	2	0.540
13	6	11.5	Right common carotid	Cannula	Left common carotid and both vertebrals ligated	I^{131}	150	3	0.335
14	7	12	Left common carotid	Cannula	Right common carotid and both vertebrals patent	I^{131}	42	3	0.467
15	7	12	Left common carotid	Cannula	Right common carotid and left vertebral ligated; right vertebral patent	I^{131}	84	5	0.278
16	7	12	Left common carotid	Cannula	Right common carotid and both vertebrals ligated	I^{131}	168	3	0.240
17	8	12.5	Right common carotid	Cannula	Left common carotid and both vertebrals patent	I^{131}	40	2	0.360
18	8	12.5	Right common carotid	Cannula	Left common carotid and right vertebral ligated; left vertebral patent	I^{131}	60	2	0.235
19	8	12.5	Right common carotid	Cannula	Left common carotid and both vertebrals ligated	I^{131}	80	4	0.148
20	9	17.5	Left common carotid	Cannula	Right common carotid and both vertebrals patent	I^{131}	80	6	0.177
21	9	17.5	Left common carotid	Cannula	Right common carotid and both vertebrals ligated	I^{131}	80	2	0.110
22	10	10	Right common carotid	Cannula	Left common carotid and both vertebrals patent	P^{32} *	72	4	0.675
23	10	10	Right common carotid	Cannula	Left common carotid and both vertebrals patent	I^{131}	120	4	0.610
24	10	10	Right common carotid	Cannula	Left common carotid and both vertebrals ligated	I^{131}	150	5	0.276
25	11	11	Right common carotid	Unexposed artery	Left common carotid and both vertebrals patent	Cr^{51} †	200	3	0.187
26	11	11	Right common carotid	Unexposed artery	Left common carotid and both vertebrals patent	I^{131}	76	4	0.135

*In aqueous solution †In 4 cc. of red blood cells

Average velocity (cm. per second)	Measured flow rate (cc. per minute)	Volume of blood collected (cc.)	Duration (minutes and seconds)	Actual flow rate (cc. per minute)	Error (%)	% increase in flow due to ligation of other vessels	Remarks
14.2	—	—	—	—	—	—	I^{131} as radioactive iodinated serum albumin
9.68	110	80	0′ 45″	107	+2.6	—	
31.0	321	220	0′ 39.6″	334	−3.9	—	
12.6	127.50	125	1′ 09.3″	125	+3.9	—	
—	—	—	—	—	—	—	Blood collected on moving strips of absorbent paper to detect distribution of isotope in artery
—	—	—	—	—	—	—	
9.21	95.5	—	—	—	—	—	
30.3	322	263	0′ 30″	526	−0.6	—	
40.6	420	235	0′ 35″	403	+4.3	—	
17.4	180	—	—	—	—	—	Right common carotid found ligated during surgery
41.6	431	—	—	—	—	148	
13.4	139	—	—	—	—	—	
18.0	187	—	—	—	—	61.3	
12.9	134	—	—	—	—	—	
21.7	242	—	—	—	—	68.4	
25.1	261	—	—	—	—	95	
16.8	174	—	—	—	—	—	
25.7	266	—	—	—	—	53.2	
40.9	423	—	—	—	—	144	
33.8	354	175	0′ 30.05″	346	+2.1	—	
55.4	574	—	—	—	—	65.6	Dog was bled but no volumetric reading was obtained
8.95	93.5	—	—	—	—	—	Use of P^{32} to test effect of serum albumin in isotope on bolus formation and difference in flow velocity measurement. Difference of 10.8% in velocity was found.
9.90	102.5	—	—	—	—	—	
21.9	227	—	—	—	—	145	
32.2	—	—	—	—	—	—	Tagged red blood cells used to test coring phenomenon of cells —velocity of cells is 68.2% higher than average velocity measured using I^{131}.
19.2	—	—	—	—	—	—	

EXPERIMENTAL DATA

In 11 dogs 10 to 24 kg. in weight, calibration data were obtained as follows. Siliconized plastic tubing of known diameter and 30 in. in length was connected in series in the exposed carotid artery in the neck. Measurements were made of the blood velocity within the siliconized tubing by the use of the double-beamed collimator. Clotting was prevented for a period of four to six hours in the siliconized tubing by heparinization of the experimental animal. After measurements were made with the tubing in situ, the distal end of the tubing was removed from the arterial lumen and velocity measurements were repeated over the tubing as blood was collected from the open end. The quantity of blood collected for a particular time interval was known, as was the cross-sectional area of the tubing. With these known quantities, absolute values for blood flow were obtained and compared with computed values using the measurements obtained with the double-beamed collimator. The size of the open end of the siliconized tubing was controlled with an adjustable clamp so that blood flow could be manually controlled to minimize shock in the experimental animal from acute blood loss. Values for absolute blood flow obtained by these two methods were then compared for accuracy. RISA was injected into the forelimb vein of the dog after all preparations were completed for recording the radioactivity over the exposed carotid artery.

In dog No. 9, it was found that measurements obtained in the intact tubing connected in series in the carotid artery were 354 cc. per minute. The tubing was then disconnected at its distal end, and an adjustable clamp was put on the tubing and tightened until a smooth but slow flow was obtained from the open end. A second injection of 80 μc. of RISA was then given the animal, and a second measurement of velocity was made over the tubing while at the same time the blood was collected in a measuring cylinder during a thirty-second interval. The velocity measurement over the tubing was calculated at 33.8 cm. per second; 175 cc. of blood was collected during the thirty-second interval. Blood flow calculated from the actual quantity collected and the time of collection was 346 cc. per minute. Blood flow calculated on the basis of velocity measurements by the collimator and the known cross-sectional area of the tubing were 354 cc. per minute. The error in this particular instance was 2.1%. The actual measured flow and the calculated blood flow in these experiments corresponded with an error of $\pm$ 4.3%.

In dogs 2, 3, 4, and 9, recordings showed that as many as 6 characteristic curves could be obtained from a single isotope injection so that the velocity of flow could be measured during several heart beats. The deviation from the average obtained from multiple readings from a single injection was as much as 20 to 25%, because of pulsatile flow. However, the average computed flow from these multiple readings was always within 4.3% of the actual measured flow in these experiments.

It was concluded that globules of RISA moved in the blood stream at approximately the average velocity of blood. Distribution of the isotope in the blood was checked by injecting one of the animals with the isotope and collecting blood from the tubing in the carotid artery onto a strip of absorbent paper moving at a constant velocity (Tests 5 and 6). After drying of the blood, the strip was checked for activity, and it was found that there were isolated points of relatively high isotope activity. This indicated that the isotope temporarily may move in separate boli, and, keeping this in mind, one realizes that the isotope can be expected to give several calculations within a short time interval after a single injection.

DISCUSSION

The anatomic characteristics of the carotid vessels in the neck are important. The common carotid artery in the dog is 6 to 8 cm. long and divides into the internal and external carotid vessels at the junction of the middle and upper third of the neck. Of the 2 carotid vessels, the external carotid artery in the dog is the main contributor to the cerebral flow, the internal carotid being quite small. Other vessels in the vicinity that are important carriers of blood are the jugular system of veins and the vertebral artery and veins. The isotope content of the vertebral artery does not appear to influence counts as concerns the carotid artery, and the isotope content of the venous blood would lag behind the arterial count by four

to seven seconds, or the circulation time from the carotid into the brain and back into the venous side and the jugular veins. With a gamma emitter such as RISA and the collimator cone placed upon the pulsating carotid, recording appears to be mostly due to activity in the carotid artery and not to activity in other vessels in the vicinity.

In man, the common carotid artery is 10 to 12 cm. long and is divided into the external and internal carotid branches at the junction of the upper and middle thirds of the neck. The internal carotid artery in the normal person is almost twice the size of the external carotid branch. It continues up the neck as a nonbranching solid vessel. The external carotid artery, on the other hand, begins to divide, usually within a centimeter or so.

Although collimator cones may be placed upon the common carotid artery with recording of blood flow by this technic, a more practical and worthwhile measurement would be to show good blood flow between the common carotid and the internal carotid arteries; conversely, if the internal carotid artery is partially or completely occluded, lag of circulation time or an actual abnormality of count on the affected side (compared with the opposite side) should be obtained. It is thought that the branching external carotid artery may present no serious complications in calculation, but clinically it is also known that, when the internal carotid artery is completely or partially shut off, the external carotid artery may become enlarged. It is not clear whether, under these circumstances, collimator cones applied on the common carotid artery in the region of the internal carotid may not reflect the presence of internal carotid stenosis or occlusion if the external carotid has become larger. Experimental work on exposed human vessels in the neck undoubtedly would be of great help in noting the importance of these statements.

In man, the vertebral artery may be rather large but is farther away from the collimator cone than the carotid artery over which the collimator may be applied. The jugular vein is a huge structure, and it may be possible to obtain circulation time through the brain by recording the isotopic activity over the common carotid–internal carotid area followed by the isotopic activity in the region of the jugular bulb in a position immediately below and a little in front of the mastoid process on a given side. Circulation time may be important in some instances with increased vascular resistance in the brain and associated nervous disease. Circulation time also may be definitely impaired in the presence of partial occlusion of stenotic lesions in the larger vessels supplying the brain. The circulation time may be tested on the one as well as on the other side.

In human experience, the value of this method would be definitely enhanced if recordings could be made of the common carotid and internal carotid artery, with a view to showing any changes between these two vessels because of the presence of stenotic or occlusive disease involving the junction of the common and internal carotid arteries.

A collimator head or cone which is small enough to lend itself to easy use in the operating room may be used for confirmation. By this technic, one may be able to get valuable information concerning the accuracy of the method.

SUMMARY

1. Experimental data are presented to calculate blood flow in the carotid artery in the neck of the dog.

2. A collimator divided into two detecting parts or cones for the recording of radioactivity in the carotid artery with a known distance between the two cones was utilized.

3. The accuracy of this method of recording blood flow in the carotid artery in the dog has been within 5%.

4. It is hoped that this technic may offer a practical method to scan blood flow on the two sides of the neck in human beings without the need for surgical exposure of the neck vessels.

REFERENCES

1. Oldendorf, W. H., and Crandall, P. H.: Bilateral cerebral circulation curves obtained by intravenous injection of radioisotopes. J. Neurosurg. 18:195, 1961.
2. Hardesty, W. H., Roberts, B., Toole, J. F., and Royster, H. P.: Studies of carotid-artery blood flow in man. New England J. Med. 263:944, 1960.

Evaluation of UK-738 in the treatment of extrapyramidal disorders

Preliminary communication

Tamas Frigyesi, M.D.

BELLADONNA ALKALOIDS have long been used for the treatment of parkinsonism.[1] Dillenberg and associates,[2] in reviewing the clinical results obtained from various drugs used in the "Bulgarian Treatment," stated that none of the preparations from root extract had any distinct advantage over the others.

In the past fifteen years, several synthetic compounds have been introduced for the treatment of parkinsonism. Many of these drugs have been reported to be superior to the natural belladonna alkaloids in that they exhibited selective effect on rigidity and tremor, in contrast to the complex central and peripheral pharmacodynamic properties of atropine.

UK-738 (methylbenztropine hydrobromide) is one of the most recent members of this group of synthetic compounds. Besides its anticholinergic effect, it has antiserotonin properties. The latter is noteworthy, since certain components of the tryptophan and catecholamine metabolism have recently been implicated in the pathophysiology of extrapyramidal disorders.[3–7]

A complete study of the comparative antiserotonin activity of anticholinergic compounds is not yet available. Grünthal[8] first reported the alleviation of posttraumatic hyperkinesis, double athetosis, and the tremor of Benedict's syndrome by caramiphen. Since then, extrapyramidal motor disturbances other than parkinsonism have been shown to respond to several of the synthetic anticholinergic compounds.[9,10] It appears that those anticholinergic compounds with significant antiserotonin properties exert some distinct effects that are not seen with weaker serotonin antagonists.[6,11,12]

The present study was designated to evaluate the effectiveness of UK-738 on various extrapyramidal disorders. Trihexyphenidyl and benztropine methanesulfonate, which have proved anticholinergic and unproved antiserotonin effects, served as controls.

PHARMACOLOGY

The structural formula of UK-738 (n-ethyl-nortropine-benzhydryl-ether-hydrobromide) can be seen in the figure.

Pharmacologic analysis[13] of UK-738 indicates that it possesses a weaker peripheral and a stronger central anticholinergic effect than atropine. Its spasmolytic, mydriasis-inducing, and cardiac effects and inhibition of pilocarpine-evoked salivation are about 10 times weaker than that of atropine. The central effects of UK-738 (inhibition of cataleptic reactions produced by phenothiazines, potentiation of pentothal anesthesia, and potentiation of the excitatory effect of amphetamine) are stronger than those of atropine. Thus, it may be designated as an anticholinergic compound with a predominantly central activity.

The acute toxicity of UK-738 in mice, rats, and rabbits, consisting of convulsions followed by respiratory arrest, appears to be much higher than that of atropine. The chronic toxicity is comparable to atropine.

On the isolated rat uterus, UK-738 in concentrations of 0.4 to 0.6 mg. per liter reduces the contractions induced by serotonin.

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This study was aided in part by a grant from Sandoz Pharmaceuticals, Hanover, N.J.

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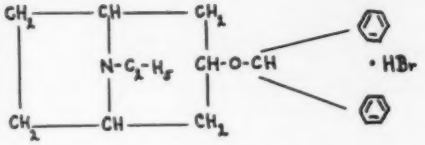
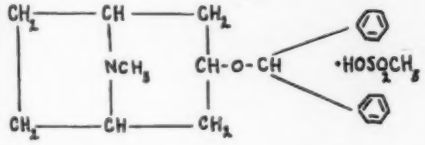


UK-738



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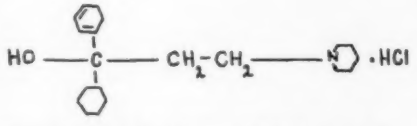

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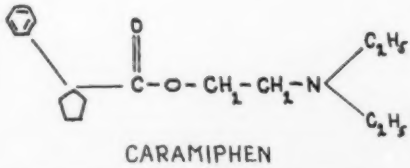

CARAMIPHEN

Structural formulas of UK-738, benztropine methanesulfonate, trihexyphenidyl hydrochloride, and caramiphen. UK-738 differs from benztropine methanesulfonate only in that a methyl group is substituted for an ethyl radical.

MATERIAL AND METHODS

This study was comprised of 84 inpatients at Pineland Hospital and Training Center. Table 1 shows the sex, age distribution, and diagnosis of the patients.

Before this study was begun, 54 patients received trihexyphenidyl and benztropine methanesulfonate. UK-738 was introduced to the patients' therapy by means of gradual substitution. The usual starting dose was 2 mg. twice daily; the average dose was 6 mg. daily and in no instance exceeded 12 mg. daily.

The remaining 30 patients had not been receiving any medication immediately preceding the administration of UK-738. The doses of UK-738 in this group were similar to those in the previous one. These patients received trihexyphenidyl and benztropine methanesulfonate after the trial with UK-738.

The patients had no knowledge of changes in medication. However, it was not feasible in the current study to make use of double-blind technic.

The observation period before the institution of UK-738 treatment was three months. The observation of patients treated with UK-738 lasted three to eight months. On each visit, the results of examinations were recorded without reference to previous examination.

The evaluation of degree of changes in extrapyramidal motor disturbances is hindered when based entirely upon subjective means, such as the investigator's recollection of the patient's earlier condition. Therefore, after the examinations were completed, motion pictures were obtained of 50 patients before medication and at various stages of observation. Films were taken once every fortnight or as indicated by

TABLE 1
AGE DISTRIBUTION, SEX, AND DIAGNOSES OF 84 PATIENTS TREATED WITH UK-738

	Number of patients	
Age (years)		
8 - 14	12	
15 - 49	56	
50 - 70	16	
Sex		
Male	50	
Female	34	
Diagnosis		
Parkinsonism	37	
Drug-induced		12
Postencephalitic		10
Idiopathic		15
Athetosis	39	
Hemi		24
Double		15
Myoclonus	2	
Intention (cerebellar) tremor	6	

clinical changes or by changes in therapy; 16-mm. color film was used. The single recordings were 25 to 100 ft. long—one to four minutes' viewing time. The comparison of motion pictures and the evaluation of changes, if any, were made by the investigator and in 17 cases by independent panels. Whenever there was a disagreement regarding the patient's condition, the least favorable classification was recorded.

The effect of UK-738 was evaluated only by virtue of objective changes. The reliability of the self-observation of patients with middle and high-grade oligophrenia is frequently doubtful. Many subjects of this study did not verbalize at all or not coherently. Therefore, subjective changes were not a guide in the evaluation of this drug.

RESULTS

When the results of treatment with UK-738 are compared to the efficacy of trihexyphenidyl and benztropine methanesulfonate, significant differences can be noted (Table 2). UK-738 appears to be a weaker antiparkinsonism drug than the other 2 compounds. It is effective in drug-induced parkinsonism. Its limited therapeutic value in other forms of parkinsonism lies in the fact that it is effective against rigidity and has no side effects. In athetosis, intention (cerebellar) tremor, and myoclonus, however, UK-738 exerts a clear therapeutic effect in contrast to trihexyphenidyl and benztropine methanesulfonate.

The manifestations of this therapeutic effect on athetosis were as follows: [1] diminution of rigidity, [2] decrease of involuntary movements, and [3] greatly increased volitional motor ability, even without a significant change in rigidity and involuntary movement. The last was not considered to be a practice effect. These patients had participated in occupational and physical therapy activities for a long time and had reached the level of maximal performance that could be obtained by exercise. The increased motor performance of patients with athetosis is illustrated by the following case histories.

Case 1. A 40-year-old white man had "slept for a month after his birth" and could not be aroused during this period. When he recovered from this state, he was found to have left hemiparkinsonism and right hemiathetosis. During the past twenty-five years, various antiparkinsonism drugs were administered without any significant benefit, except for a minimal decrease of the left-sided tremor. He had never been capable of any volitional motor action with his right upper extremity.

TABLE 2

COMPARATIVE EFFICACY OF UK-738, TRIHEXYPHENIDYL, AND BENZTROPINE METHANESULFONATE IN EXTRAPYRAMIDAL DISORDERS

Diagnosis	*Sign*	*Number of patients*	*UK-738*		*Trihexyphenidyl*		*Benztropine methanesulfonate*	
			A*	B†	A	B	A	B
Parkinsonism		37						
Drug-induced	Tremor	12	4	4	4	8	3	7
	Rigidity		0	12	4	7	5	7
Postencephalitic	Tremor	10	3	1	2	6	3	3
	Rigidity		1	9	2	5	3	4
Idiopathic	Tremor	15	2	1	2	7	3	2
	Rigidity		7	4	2	4	3	5
Athetosis		39						
Hemi	Involuntary movements and rigidity	24	7	8	2	0	0	0
Double		15	6	1	0	0	0	0
Other		8						
	Myoclonus	2	1	1	0	0	0	0
	Intention tremor	6	1	3	0	0	0	0

* Column A indicates number of patients showing detectable improvement.
† Column B indicates number of patients showing marked improvement.

For the past ten years, he has attended occupational therapy and developed a skill for drawing with his left hand. He had received benztropine methanesulfonate for the last ten months. This drug was gradually supplanted by UK-738. By the third week of this regime, the patient was able to draw with his right hand, though the drawings did not and still do not compare with those made with his left hand. UK-738 treatment was discontinued after five weeks. In the ensuing three weeks, he received no medication. Meanwhile, he gradually lost his ability to draw with either hand. For the next six weeks, benztropine methanesulfonate was reinstituted. During this time, he was able to draw with his left but not with his right hand. Then benztropine methanesulfonate was once more gradually replaced by UK-738. From the second week on, the patient was once again able to draw with his right hand also.

Case 2. A 31-year-old white woman had meningoencephalitis in her infancy. Double athetosis was first noted when she was recovering from this acute episode. In her early childhood, she received extensive physical therapy; she learned how to walk and to hold small objects with the first and second toes of both feet and, by this means, to feed herself. She also learned to write with her feet. However, she has never been capable of performing any volitional act with her upper extremities. Various antiparkinsonism drugs have been tried without any benefit. During this study, she received 6 to 12 mg. of UK-738 daily. Once every week, the patient was offered a spoon and was asked to hold it in her hand and place it in her mouth. In the ninth week, after gradual improvement, she reached a point where, though in a clumsy manner, she was able to pick up a spoon from the table, dip it into a bowl of cereal, and place the spoonful in her mouth. This activity has not yet become the patient's everyday routine; apart from this once-a-week experiment, she was not encouraged to use her hands.

Case 3. A 31-year-old white woman displayed double athetosis since birth. She exhibited almost constant movements during her waking hours. There had been only minimal variations of symptoms during the observation period before administration of UK-738 and also in the last five years, according to the hospital records. She had been confined to bed throughout her life. Placement in a wheel chair was restricted, even with protective restraints, because she would slide under the belts. She had no command over her upper extremities. Trials with several antiparkinsonism drugs were without apparent benefit. When UK-738 treatment was instituted, from the second week on there was a gradual diminishing of the involuntary movements. From the eighth week on, there were longer periods when her upper extremities were free of athetoid movements. In the meantime, she gained weight. Once a week, the patient was asked, while lying in bed, to attempt to sit up. Except for this request, she was not encouraged to perform this activity. At the end of the fifth week, the patient was able to sit up with assistance and to stay in a sitting position without assistance for several minutes. At the end of the ninth week, she was able, though with difficulty, to sit up and remain sitting as long as she wished, unaided. A remarkable feature was that she developed so much control over her right arm that, while lying on her left side, she was able to feed herself without assistance and was able to use a spoon without spilling food.

The small number of patients does not permit one to formulate a definite opinion regarding the therapeutic value of UK-738 in myoclonus and intention (cerebellar) tremor. Nevertheless, it is noteworthy that UK-738 appeared to be effective in these categories. The patients with myoclonus also suffered from convulsive disorders and were receiving continuous anticonvulsant therapy. UK-738 was added to their previous treatment. It alleviated the involuntary movements which had previously been troublesome.

Side effects in this series were conspicuous by their absence. No case of excessive oral dryness, visual blurring, headache, giddiness, or tachycardia was observed. These observations agree with those of May, Ruland, and Gold,[14] who also found UK-738 to be free from side effects. Older patients tolerated UK-738 as well as the younger age group.

One patient died during this study. Autopsy revealed hemorrhagic hepatitis with pericholangitic changes and hyalinization of vascular walls. Whether this was in any way related to the UK-738 administration cannot be stated at this time.

DISCUSSION

So far, 84 patients have been tested for a sufficiently long period to permit preliminary conclusions to be drawn on the apparent efficacy of UK-738. The lack of double-blind safeguards might raise a possibility of bias. However, some of the results reported above were so impressive that it was felt they could not be due entirely to errors in observation. As far as these initial results are concerned, it appears that the role of UK-738 in the treatment of extrapyramidal motor disturbances is a limited one. Nevertheless, the effectiveness of UK-738 in the treatment of athetosis is

considered sufficiently encouraging to warrant this report.

The clinical qualities of UK-738 resemble those of caramiphen. Bovet and Longo[15] indicated that the mechanism of action of caramiphen in parkinsonism is different from that of atropine and scopolamine. The antiserotonin properties of caramiphen appear to be comparable to those of UK-738. Consequently, it is tempting to hypothesize that the similar clinical qualities of these compounds stem from their common chemical properties. This hypothesis is in agreement with the notion that the etiologic component of certain forms of extrapyramidal diseases is a chronic defect of metabolism.[16,17] Barbeau[3] and Ehringer and Hornykiewicz[7] have related certain changes of catecholamines in the urine and brain to the altered functioning of the extrapyramidal system. Further studies in the way tryptophan metabolites act on this system seem indicated.

SUMMARY

1. The effect of UK-738 (methylbenztropine hydrobromide), a synthetic anticholinergic with antiserotonin properties, was evaluated in 84 patients suffering from extrapyramidal disorders. Trihexyphenidyl and benztropine methanesulfonate served as controls.

2. UK-738 appeared to be a weaker antiparkinsonism drug than the other two compounds.

3. In athetosis, intention (cerebellar) tremor, and myoclonus, UK-738 exerted a clear therapeutic effect in contrast to trihexyphenidyl and benztropine methanesulfonate.

4. Side effects of UK-738 were not observed.

5. It is postulated that the clinical characteristics of the effect of UK-738 are related to its antiserotonin properties.

The author wishes to extend his appreciation to David Harkins, R.P.T., and Doris Cushing, R.N., for their technical assistance and to Frank Graig, M.D., and Dr. Albert J. Pinnerstein for their advice.

UK-738 was supplied by Sandoz Pharmaceuticals, Hanover, N.J.

REFERENCES

1. Panegrossi, G.: Sulla cosi detta "cura bulgara" del parkinsonismo postencefalitico. (Nota preliminare.) Policlinico (sez. pract.) 42:56, 1935.
2. Dillenberg, S. M., Merritt, H. H., Price, J. C., von Witzleben, N. D., Neal, J. B., Doshay, L. H., Ford, T., and Vollmer, H.: The treatment of paralysis agitans with drugs. A. Res. Nerv. & Ment. Dis., Proc. 21:542, 1942.
3. Barbeau, A.: Preliminary observations on abnormal catecholamine metabolism in basal ganglia diseases. Neurology 10:446, 1960.
4. Barbeau, A.: Dopamine and basal ganglia diseases. Arch. Neurol. 4:97, 1961.
5. Barbeau, A., Murphy, G. F., and Sourkes, T. L.: Excretion of dopamine in diseases of basal ganglia. Science 133:1706, 1961.
6. Stern, P., Ratkovic, D., and Fuks, Z.: Pharmacological influences on intentional tremor. Arch. internal. pharmacodyn. 130:1, 1961.
7. Ehringer, H., and Hornykiewicz, O.: Distribution of noradrenalin and dopamine (3-hydroxytyramine) in human brain and their behavior in diseases of the extrapyramidal system. Klin. Wchnschr. 38:1236, 1960.
8. Grünthal, E.: Ueber Parpanit, einen neuen extrapyramidal-motorische Störungen beeinflussenden Stoff. Schweiz. med. Wchnschr. 76:1286, 1946.
9. Hartmann, K.: Erfahrungen mit dem neuen Präparat "Parpanit" bei der Behandlung von Erkrankungen des extrapyramidalen motorischen Systems. Schweiz. med. Wchnschr. 76:1289, 1946.
10. Zier, A., and Doshay, L. J.: Procyclidine hydrochloride (Kemadrin) treatment of parkinsonism. Neurology 7:485, 1957.
11. Schwab, R. S., and Chafetz, M. E.: Kemadrin in the treatment of parkinsonism, Neurology 5:273, 1955.
12. Duff, R. S.: Use of diparcol in parkinsonism. Brit. M. J. 1:613, 1949.
13. Sandoz Pharmaceuticals: Personal communication from Basel, Switzerland.
14. May, R. H., Ruland, M. B., and Gold, M. R.: Treatment of drug-induced extrapyramidal hyperkinetic reactions with UK-738 (n-ethyl-nortropine-benzhydrylether-hydrobromide) Am. J. Psychiat. 116:360, 1959.
15. Bovet, D., and Longo, V. G.: The action on nicotine-induced tremors of substances effective in parkinsonism. J. Pharmacol. & Exper. Therap. 102:22, 1951.
16. Denny-Brown, D.: Etiology. In Parkinsonism and Its Treatment, edited by L. J. Doshay. Philadelphia, J. B. Lippincott Co., 1954, pp. 24-30.
17. Doshay, L. J.: Parkinson's disease. J.A.M.A. 174: 1962, 1960.

Neural correlates of the vestibuloocular reflex

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OVER THE PAST DECADES, a number of attempts have been made to establish the existence of consistent physiologic changes in psychoses, changes which might be useful in focusing experimental investigative programs on possible neural substrate areas. Abnormal, hypoactive, or paradoxic vestibular functioning has been reported in some adult schizophrenics[1,2] and more recently in schizophrenic children.[3] The picture, as it emerges in the studies of Bender and Helme,[3] of Colbert, Markham, and Koegler, [4–6] and others on children who show psychotic symptomatology early in life, includes postural abnormalitites, "preoccupation with time, space and motion"[3] as evidenced by spontaneous whirling, toe walking,[5] and some rather marked changes in vestibuloocular function characterized by depressed or absent vestibular response to caloric and rotational tests. Hypoactivity of nystagmus responses was most marked in the younger childhood schizophrenics and responses characteristically varied from test to test, unlike the more stable patterns of controls. Relative absence of vertigo after labyrinthine stimulation was another quality noted in the patient group.

With these demonstrated vestibuloocular abnormalities as a starting point, it was proposed to search the upper brain stem and subcortical structures for sites modulating vestibuloocular responses in acute and chronic preparations. Stimulation or other manipulations of such areas would then be studied in chronic preparations for signs of abnormal behavior or mental function which simulate at cruder levels some of the aspects of human psychosis. If such areas could be found, they would very obviously be worth closer study in clinical material.

MATERIALS AND METHODS

The work was done on 70 adult cats weighing 2.5 to 3.5 kg.; 35 acute preparations produced useful information. Our initial attempts at preparing chronic animals were abandoned because of difficulty in producing consistent nystagmus and the relatively few sites that could be evaluated in each animal. On the basis of our recently gained experience, we plan to return to the chronic preparations.

A tracheal cannula was inserted under light ether anesthesia, the animal was placed in a Horsley-Clark stereotaxic frame, and bipolar side-by-side electrodes were implanted. Skin flaps and occasionally the external auditory canals were infiltrated with 1% procaine, after which ether was discontinued. The animals were maintained under local anesthesia in much the same way as are human neurosurgical patients. During recording and stimulation, the animals were awake, alert, and restrained but quiet.

Nystagmus was produced by several means: [1] A small 100-ohm resistor connected to a direct current source was placed against the bony labyrinth through the mastoid bulla or on the petrous ridge via an intracranial approach. [2] Cold water was irrigated into the middle ear. This caused the animal discomfort and was infrequently used. [3] The cat was rotated on a turntable having 6 platinum elec-

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This work was made possible by grants from the California State Mental Hygiene Department and the National Institute of Neurological Diseases and Blindness.

Read before the Section on Neuroanatomical Sciences at the thirteenth annual meeting of the American Academy of Neurology, Detroit, April 27, 1961.

trodes running in individual mercury-filled troughs. After 10 turns in twenty seconds, the rotation was stopped and after-nystagmus was recorded. [4] The medial or lateral vestibular nuclei were stimulated directly with trains of square waves of 2 to 4 volts, 100 per second, 1-msec. duration. When more than one method was used on a given cat, there was very little variation in the character of the nystagmus. On the other hand, there was considerable variation in the frequency, amplitude, and regularity of the nystagmus from cat to cat. Similar variations have been noted by us[4] and others in human material.

Nystagmus was led from needle electrodes placed in the medial and lateral recti and occasionally in other muscles; brain waves were recorded from screws tapped into the frontal, parietal, and temporal bones. The recording was done on an 8-channel Offner Type T Dynagraph. Stimulation of thalamus, diencephalon, and brain stem was performed with bipolar electrodes made of 32-gauge Nichrome wire, insulated with Beldenamel except at the tips, with an interelectrode distance of 1 mm. These were connected to a Grass 4s or an American Electronics stimulator. Stimuli were administered at 100 per second and occasionally at 50, 30, and 10 per second. Voltages varied from 2 to 6, and shock duration was 0.5 and 1 msec. Stimulation duration varied from two to ten seconds.

The cat was under constant visual inspection. Changes were noted in nystagmus, pupillary size, eyelids, nictitating membranes, body tone, movements and posture, facial expression, and presence or absence of piloerection. Occasionally, we found alterations in nystagmus could be better determined visually than electrically.

The brains of the cats were fixed in formalin and later stained by the Kluver method.

RESULTS

Subcortical and upper brain stem exploration for sites affecting vestibular nystagmus has demonstrated a number of areas which modify this activity. Several patterns of change have been noted and are referred to hereafter as *augmentation, inhibition, and regularization.*

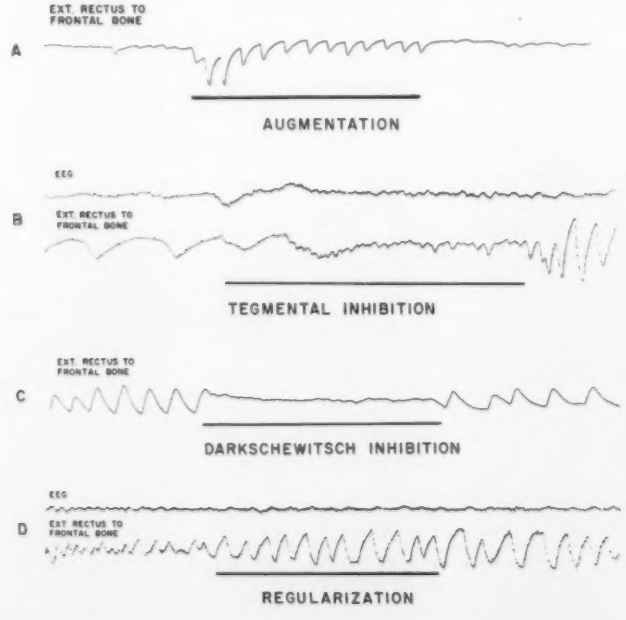

Fig. 1. Patterns of modulation of nystagmus derived from stimulation of upper brain stem and subcortical structures. [A] Augmentation. [B] Tegmental inhibition characteristic of stimulation throughout mesencephalic reticular formation and lateral hypothalamus. [C] Darkschewitsch inhibition characteristic of complete inhibition with slight ocular protrusion produced by stimulation in nucleus of Darkschewitsch. [D] Regularization (with some augmentation) characteristic of stimulation in isolated areas of dorsolateral tegmentum and thalamus (see text)

Augmentation consisted of an increase in amplitude of the fast and slow components of nystagmus as noted by direct observation of the preparation and/or on the electroencephalographic tracing (Fig. 1). Inhibition was characterized by a decrease in amplitude of the swings, often associated with marked increase in frequency of the excursions (Fig. 1). Usually, as the degree of inhibition increased, the rate rose until it became a tonic "shimmer," after which, in cases of complete inhibition (that is, lateral mesencephalic tegmentum), no further movement was seen. In the case of regularization, previously noted irregularities in timing and/or swings of the ocular beats were lessened or removed completely, the trace approximating more nearly a sinusoidal pattern for the duration of stimulation (Fig. 1).

A generally consistent pattern revealed in the data cannot gainsay the fact that the degree of variability from animal to animal was large. In some preparations, nystagmus of marked contours and long duration could be easily produced, while in others a few weak beats at best were obtained even though the physiologic state of the organism was satisfactory. Similary, there was a wide variation in the effectiveness of given centers on eye movements, suggesting marked individual differences in the effectiveness of neural systems from organism to organism.

Mesencephalic stimulation usually inhibited nystagmus, the character of the inhibition depending on the stimulation site. In general, mild inhibitory effects were obtainable in the midtectum, becoming more profound as the tegmentum was penetrated (Fig. 2). Along with these more effective degrees of inhibition, a number of autonomic and somatic responses appeared which seemed to characterize all stimulation of the upper reticular core. These phenomena included dilation of pupils, piloerection, and baring of the fangs along with arching of the back, hyperextension of the extremities, and evidence of increased general alertness. An exception to this was the nucleus of Darkschewitsch—which, as shown previously by Szentágothai and Scháb,[7] produced complete inhibition of eye movements and occasionally slight protrusion of the eye without other effects (Fig. 2). Inhibition of nystagmus here was not preceded by the high-frequency "shimmering" nystagmus seen on stimulation of the rest of the mesencephalon. In all cases where penetration of this nucleus was achieved, the effect was immediate and clear-cut, lasting for only a millimeter or two of electrode traverse, then again becoming "contaminated" by reticular effects. In our experience, no other part of the brain stem or subcortex produced an arrest as immediate, complete, and uncontaminated as the nucleus of Darkschewitsch.

Our most posterior electrode placement passed through the superior colliculus at A2, where regularization of the beat was noted in the depths of the colliculus, shutting off abruptly as the periaqueductal gray was penetrated. More rostral penetrations of the colliculi in other animals often produced mild inhibition, as already noted.

At pretectal levels, the over-all pattern remained the same except for the appearance of a consistent island of augmentatory responses just medial to the lateral geniculate, including portions of the lateral posterior, lateral dorsal, pulvinar, and suprageniculate nuclei. This corresponds to a nystagmogenic area described by Lachman, Bergmann, and Monnier.[8]

Diencephalic exploration revealed a central core of medial and midline nuclei starting caudally with the centromedian-parafascicular complex and extending anterior to the nucleus reticularis thalami, all of which appear to exert augmenting effects on nystagmus. Approximately one response out of four departed from this pattern, showing either inhibition or regularization. Such aberrant findings were usually noted in the outermost parts of this core, close to relay or association nuclei. A thin strip of augmenting effects also reached down into the hypothalamus close to midline in the distribution of fibers descending from the midline thalamic nuclei (Fig. 2). Associated with these principal effects on nystagmus was a group of more varied changes in frequency of the excursions and in the major axis of gaze about which the nystagmus occurred. Because of the highly variable and nonpredictable quality of these responses, they are not further alluded to in this communication.

Lateral to the central thalamic core just mentioned, most of the nuclear masses gave partial or complete suppression of nystagmus or were without effect. Variability throughout

the lateral and ventral nuclei was very marked, approximately 6 responses in 10 proving inhibitory to some degree, 3 being without effect, and 1 proving either regularizing or augmenting. With these reservations, the area is labeled inhibiting in Figure 2. Surrounding this area in turn was found a shell of augmenting responses. Many of these were found in the dorsolateral portions of the pulvinar, lateral dorsal, and lateral posterior nuclei and probably represented a rostral continuation of the island of augmentation noted dorsomedial to the superior geniculate body at pretectal levels. The remainder of augmenting effects coincided with the external medullary lamina, thus giving further suggestion that the thalamic reticular formation enhanced nystagmus.

The hypothalamus proved to be almost entirely inhibitory with the exception of the thin paramedian tongue of tissue thought to represent the ventral projection area of the midline thalamic nuclei. Most inhibitory sites seemed to lie within the zona incerta, fields H1 and H2, and the lateral hypothalamic area. Specific correlation with hypothalamic nuclei was not attempted. Hypothalamic inhibition was always associated with somatic and autonomic outflow phenomena, previously noticed at mesencephalic tegmental levels, though autonomic "rage" reactions seemed more obvious at these levels.

It was of interest that surrounding white matter including the internal capsule and corona radiata was also inhibitory, though com-

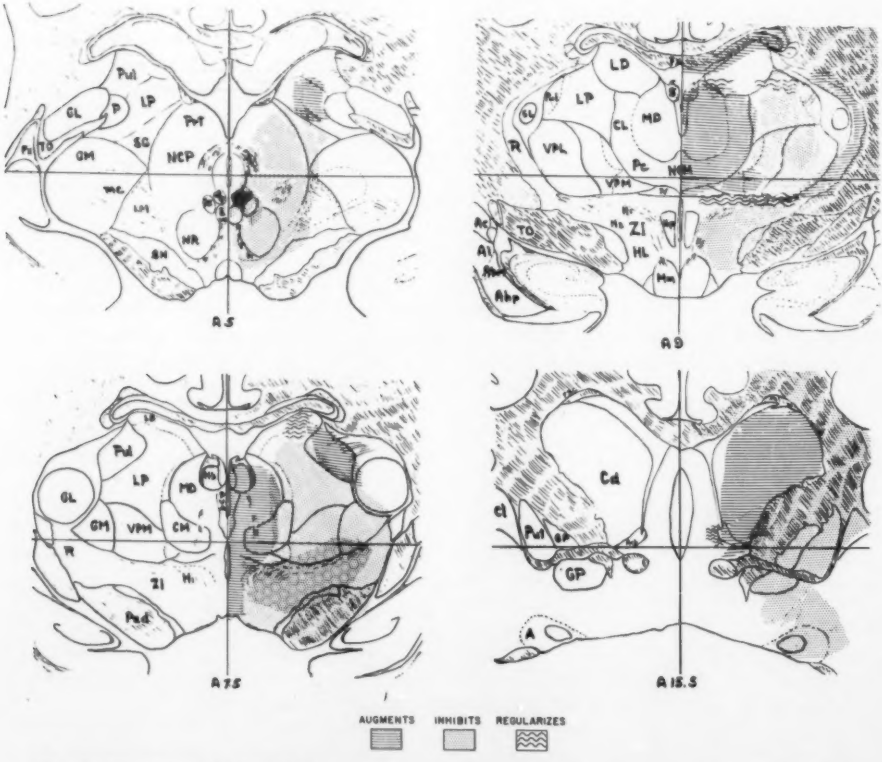

Fig. 2. Sites from which modulatory effects on nystagmus were derived. Four representative frontal sections summarizing effects of brain stimulation upon nystagmus

plete suppression was never seen. Associated effects usually included either hyperextension and increased tone in one or more body parts or fragments of motor action such as flexion of one or more joints and occasional rhythmic flexion-extension of an extremity.

The head and rostral portion of the body of the caudate were explored in some detail (Fig. 2). In 13 of 15 histologically verified tracks, caudate stimulation produced augmentation of nystagmus. No significant differences could be found between medial and lateral or rostral and caudal placements, nor did stimulation produce observable side effects in either the general state of the animal or the electroencephalogram. The 2 aberrant results were seen in the extreme ventromedial and dorsolateral corners of the caudate, respectively, and consisted of regularization of the beat with, at best, some slight suggestion of augmentation.

Of 5 histologically verified tracks through the globus pallidus, 3 gave mild to moderate inhibition and 2 were without effects; 2 clear-cut penetrations of the putamen were also without effect. Surrounding white matter remained clearly inhibitory with the apparent exception of the subcallosal fasciculus, which appeared to give augmenting responses in several penetrations.

The effects of neocortical and archicortical stimulation were not examined in this study, but it seems worth noting that 3 verified penetrations of the fornix produced augmentation; 1 also caused neocortical electroencephalographic seizure discharge as well as an overt seizure.

DISCUSSION

The significance of these data has proved difficult to evaluate. If we limit our consideration to vestibular nystagmus, it is clear that a number of upper brain stem and subcortical structures exert, under experimental conditions at least, modulatory control over vestibulooocular loops. The physiologic meaning of these effects is not clear, but certain patterns can be discerned which seem worthy of discussion.

Inhibition of vestibular nystagmus is elicited from virtually the entire tegmental core of the mesencephalon impinging somewhat on tectum. Rostral to the meso-diencephalic border, inhibition is found throughout the hypothalamus with only a narrow midline band of tissue showing other effects. Spotty inhibitory effects can also be traced forward through the general area of the thalamic relay and association nuclei from the internal medullary lamina outward almost to the external lamina, though they are by no means as convincing as the more consistent inhibition from the adjacent internal capsule and corona radiata.

If this distribution is compared with that of known neuroanatomic systems, it is found that the brain stem reticular core also ascends through the mesencephalic tegmentum and splits at the meso-diencephalic junction just caudal to the centromedian-parafascicular complex.[9–12] One leaf continues ventrally and rostrally through the zona incerta and the hypothalamus while a second bends laterally, then continues rostrally just lateral to the medial core of nonspecific thalamic nuclei.[11] It does not seem unrealistic to relate this core of inhibitory effects to the brain stem reticular formation.

Consistent inhibition of nystagmus from tegmental and hypothalamic stations is of interest in view of the fact that these areas were found by Magoun and Rhines[13] to exert *facilitatory* effects on spinal motor activity. Szentágothai also comments on this fact[7] and suggests that, within the more circumscribed frame of his tegmental exploration, no adequate explanation can be given. Careful observation of our animals and records reveal that reticular inhibition was invariably manifested by a marked decrease in amplitude of nystagmus (occasionally to the point of apparent arrest) with coordinate increase in rate of eye movements until they were sufficiently small and rapid as to show only a very fine tremor or shimmer often associated with slight enophthalmos.

Such findings suggest that the observed reticular effects may actually be facilitatory after all, having increased the degree of tension in all extraocular muscles without reciprocal patterning, arresting the movement and pulling the eye somewhat deeper into the orbital cavity under simultaneous facilitatory barrage to all extraocular muscles.

Inhibition resulting from stimulation of the nucleus of Darkschewitsch appears to differ from the former in important respects. The

inhibitory effect on nystagmus appears unique in that there are no accompanying phenomena such as increased body tone, tegmental reactions, and autonomic effects. Upon stimulation, there is abrupt cessation of all eye movements and often slight protrusion of the eye, a fact noted previously by Szentágothai,[7] with whose interpretation we agree insofar as this probably represents complete, nonreciprocal inhibition of all extraocular muscles.

The connections which underly this unique inhibitory neural mechanism remain unclear. First described in 1885,[14] Darkschewitsch's nucleus was differentiated from the immediately adjacent interstitial nucleus by Ramón y Cajal.[15] Although the latter center has recently been found by Pompeiano and Walberg[16] to project to the medial vestibular nucleus, the fate of axons of Darkschewitsch's nucleus remains unknown. Recent degeneration studies[7,16] indicate that they are not carried caudally in the medial longitudinal fasciculus, nor do they project the less-than-a-millimeter distance to the oculomotor nucleus. Szentágothai rejects the idea of intercalated neurons between this inhibitory center and the third nerve nucleus, in part, because of the small distance (as little as 200 μ) between them. Although no satisfactory structural studies on this relationship exist, we would not feel so limited as Szentágothai in invoking intercalated neurons on the basis of short distance alone. It is tempting to hypoth-

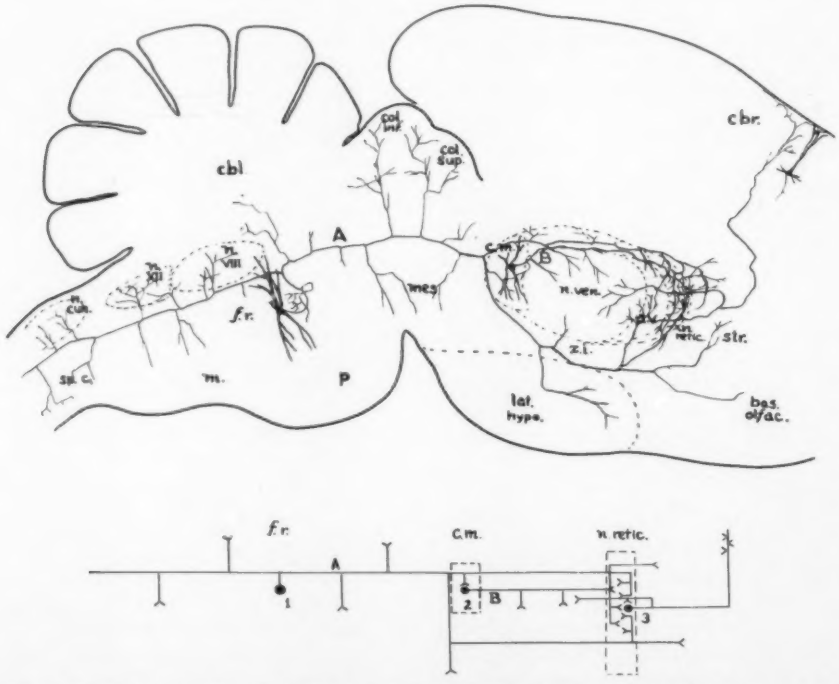

Fig. 3. Sagittal section through brain of 10-day-old rat. Drawing from single thick section of rat brain stained by method of Golgi which shows general orientation of brain stem reticular core (A) and thalamic reticular formation (B). Note that system A extends throughout most of lower stem as epitomized by axon system of single pontine reticular cell, splits caudal to centromedian nucleus (c.m.), then projects rostrally through zona incerta portion of hypothalamus, as well as laterally, and in parallel with projection of thalamic reticular system as epitomized by single cell in centromedian nucleus. From Scheibel and Scheibel,[49] with permission of Grune & Stratton, Inc.

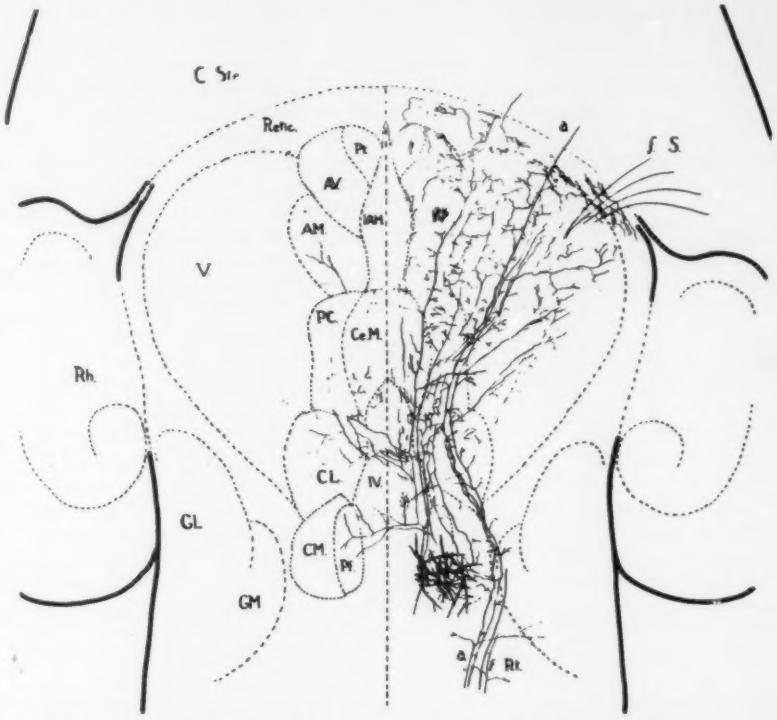

Fig. 4. Horizontal sagittal section through thalamus of 12-day-old mouse. Drawing from single thick section of mouse brain stained by method of Golgi. Thalamic reticular formation is seen as an axon system arising in centromedian (CM.) parafascicular (Pf.) complex and running rostrally to nucleus reticularis thalami (Retic.) and beyond, into corpus striatum (C. Str.). Running laterally and parallel to this system are long ascending fibers from brain stem reticular core (f. Rt.) First system runs through medial group of nonspecific intralaminar nuclei. Second is more externally placed and runs in part through more laterally lying nonspecific nuclei and through some of association and relay nuclei. From Scheibel and Scheibel,[11] with permission of Little, Brown & Co.

esize participation by short axoned elements in the adjacement periaqueductal gray or reticular tegmentum, but speculation must await Golgi studies now in progress.

In virtually all cases in the present study, stimulation at 50 to 100 per second in white matter such as the corona radiata, internal capsule, and basis pedunculi produced varying degrees of inhibition of nystagmus, often in association with changes of body tone and/or fragments of motor activity. These responses are considered comparable to effects on general motor activity noted by Peacock[17] and Forman and Ward.[18] We must assume that, although a stimulating electrode advancing through white matter at thalamic or basal ganglionar levels will be likely to stimulate fibers from many systems in the closely packed white substance, still a very considerable proportion of them will be descending components from cortical stations. A considerable body of evidence[19–23] points to the role of cortical tissue as predominantly inhibitory over downstream mechanisms. We must assume that stimulation points in white matter almost invariably included corticifugal axons, stimu-

lation of which produced similar downstream effects.

The fornix, largely (although not entirely) corticifugal from archicortical hippocampal tissue, represents an exception. On our three verified penetrations and stimulations of the fornix, marked augmentation of nystagmus was noted. These results recall observations of Forman and Ward,[18] who noted that cats became tense and overactive and showed increased licking and chewing movements on stimulation of the fornix and septum pellucidum. The mechanisms involved may well have been different.

It has already been indicated that the central nystagmus-augmenting portion of the thalamus lies within that group of medial and midline nuclei thought to make up the nonspecific thalamic projection system or thalamic integrating core.[25] It has previously been shown by Sharpless and Jasper[24] that lower reticular mechanisms are slower in action and concerned primarily with tonic activities, while the upper, diencephalic system, more labile and rapidly acting, is concerned with phasic actions. In addition, the former drops out first in habituation studies; the latter shows habituation only after many more repetitions. Another important difference between the systems was demonstrated by Rothballer,[25] who showed that chlorpromazine blocks the action of the tonic, epinephrine-sensitive system without affecting the rapid phasic mechanism. It would now seem from present data that patterns of modulation of the vestibuloocular reflex might represent another mode of physiologic differentiation between these two nonspecific systems.

Augmentation of nystagmus, as already indicated, involves increased amplitude of ocular excursions, often—though not always—associated with some slowing in the rhythm. The fact that the alternating sequences are maintained indicates that the facilitative output is being fed into extraocular muscle control mechanisms reciprocally, so that basic patterns of activity are modulated rather than destroyed. The nature of neural circuitry involved in an alternating reflex phenomenon like nystagmus remains unknown, although Lorente de Nó[26] has suggested that discontinuous series of inhibitory impulses set up by collateral links to adjacent reticular mechanisms and sequenced back to ocular motoneurons may provide the necessary substrate. In any case, it would seem that augmenting systems such as the diencephalic core and caudate work complementarily with vestibuloocular arcs, whereas inhibiting or suppressing systems compete with or inactivate them.

Although insufficient data exist to relate, causally, the nonspecific diencephalic core to psychotic manifestations in the human subject, a group of data suggests its relationship to higher aspects of neural function. Remarkably widespread projection of this system to the cerebral cortex[27] and its ability to control electrical aspects of cortical dendritic activity[28] in recruitment[29] suggest crucial thalamocortical interrelations. Arrest phenomena after intralaminar stimulation as described by Hunter and Jasper,[30] the sleep reactions of Hess,[31] and petit mal-like configurations following 3-per-second stimulation of this system reported by Jasper and Droogleever-Fortuyn[32] are also suggestive. It is interesting that a system apparently concerned with a number of phenomena related to sleep-wakefulness patterns and the varieties of conscious experience should also manifest consistent effects on a downstream reflex, especially when both of these kinds of activity may be involved in the clinical syndromes at issue.

Similar comments apply to the caudate nucleus, which our data show is at least equally effective in augmenting (and occasionally regularizing) vestibuloocular responses. Though much has been written about descending corticocaudate connections and the caudatopallidal outflow, until recently little was known about ascending reticulocaudate connections from the rostral portion of the thalamic reticular formation and of caudatal projections (direct or indirect) upon cortex. In addition to its important role in downstream extrapyramidal effects, the caudate is now known to represent an important station in the thalamic reticular projection upon the cortex, as demonstrated anatomically by Rose and Woolsey,[27] Nauta and Kuypers,[10] the Scheibels,[11] and others and physiologically by Nashold, Hanbery, and Olszewski.[33] Anatomic evidence for a direct caudatocortical link is confusing and has recently been denied by Voneida's findings in

cat and monkey.[34] However, a more indirect link is suggested by the discovery by Nauta and Mehler[35] that the supposed pallidohypothalamic bundle actually projects to centromedian, thereby furnishing a somewhat longer latency relay from striatum to cortex via nonspecific thalamic relays.

Several lines of evidence point to complex and often antithetic results from caudate stimulation, depending on stimulus parameters involved. Slow 5- to 12-per-second stimuli which demonstrate inhibitory aspects of caudatal function produced sleepy, inert, sphinx-like, or catatonic behavior for Akert and Andersson,[36] Heath and Hodes,[37] Buchwald and Ervin,[38] and others. Similarly, injection of alumina cream[39] or deposition of crystalline cholinergic drugs[40] produced lethargic, nonresponsive animals which, in the hands of Stevens, Kim, and MacLean,[40] failed to maintain conditioned avoidance responses. Bilateral caudate lesions produced similar deficits in conditional responses for Gomez, Thompson, and Mettler[41] and, for Knott, Ingram, and Correll,[42] transient disturbances in conditioned approach responses. Akert and Andersson[36] in particular have described animals with bilateral lesions showing extensive loss in spontaneous motor activity which are either unmoved by or else automaton-like in their reactions to sensory stimulation.

Other modes of caudatal stimulation have produced facilitative responses. As early as 1873, Nothnagel[43,44] described the injection of corrosive fluids into the caudate nucleus bilaterally, producing obstinate locomotor activity directed straight ahead. In the same year, Ferrier[45] was recording that faradization of one caudate produced contralateral bending of the head and body. The former findings of forced progression have been repeated more recently by Mettler and Mettler,[19] while contraversive phenomena after caudate stimulation at frequencies of 30 to 60 per second have been redescribed by Forman and Ward,[18] Akert and Andersson,[36] and Buchwald and Ervin.[38] Significantly, previously learned behavioral responses were not interfered with by such stimuli.[40]

A possible explanation for this bimodal pattern of caudate response is suggested by Stevens and associates.[40] Histologic studies by Ramón y Cajal[15] showed the presence of two separate cell populations, medium sized and small, believed by the Vogts[46] to facilitate and to inhibit body movements, respectively. Mettler, Hovde, and Grundfest[47] reported slowly conducting caudate elements incapable of responding to 40- to 60-per-second frequencies but sensitive to slower ones. Stevens and her group[40] suggested, accordingly, that the increased alertness and circling which accompanied fast frequencies or the early phases of chemical stimulation were facilitatory effects mediated by the large-cell population. Conversely, slow frequency stimulation and late chemical effects which produced akinetic, torpid animals devoid of conditioned responses activated small-cell groups with inhibitory functions. Since our usual caudate stimulus frequency was 100 per second, the consistent enhancement of nystagmus which we observed might be considered, within the framework of earlier findings, a true facilitatory effect. Not only did caudate-enhanced nystagmus often persist well after cessation of caudatal stimulation, but also, on occasion, caudate stimulation was able, by itself, to induce nystagmus some seconds after cessation of vestibular stimulation. This suggests that caudate effects not only enhance but summate with vestibular stimulation, as was shown by Delmas-Marsalet, Bergouignan, and Verger[48] for ipsilateral destructive lesions in both structures.

On the basis of considerable experimental work, it can be concluded that the caudate has both an augmenting and an inhibiting influence on certain motor patterns. The facilitatory effects are of at least 2 types. [1] The present paper suggests the caudate exerts a facilitatory influence on the vestibuloocular reflex. The site of action is unclear; it may be in the midbrain tegmentum, working through some pathway other than the nucleus of Darkschewitsch. It is also possible the caudate exerts its effect through the vestibular nucleus. [2] The circling and turning phenomena on caudate stimulation imply a facilitatory effect on head-on-neck and neck-on-body postural reflexes. The work of Delmas-Marsalet and associates[48] indicates a summating effect of forced turning by combined caudate and vestibular nucleus lesions and also suggests that the effects of the caudate on these postural re-

flexes may be mediated through the same paths used by the vestibular projections.

Even though the midbrain preparation seems to have intact head-on-neck and neck-on-body reflexes and vestibuloocular responses, the caudate may exert some control over these two reflex patterns, tending to orient the animal in space.

It may be of more than passing interest that manipulation of caudate tissue, whether involving the production of lesions, injection of cholinergic drugs, or stimulation at fast and at slow frequencies, produces signs reminiscent of those seen in psychoses. The postural abnormalities, predilection for circling behavior, forced movement, and "spinning" described by Bender and Helme[3] and erratic hypoplastic vestibular responses on the one hand; and autistic, withdrawn, nonresponsive, catatonic, or even semicomatose behavior on the other, all recognized as possible stigmata of "childhood schizophrenia," resemble the experimental preparations described above. Although it is obviously premature to suggest clear relationships between thalamocaudate activity and certain types of schizophrenic syndromes, further investigation in this area is certainly indicated. It has not yet been demonstrated, for instance, that defective caudate function—whatever the cause—results in hypofunction or dysfunction of the vestibuloocular reflex arc as described in autistic children,[6] which provided a starting point for this investigation.

SUMMARY

The high incidence of vestibuloocular abnormalities in schizophrenic children suggested the advisability of searching brain stem and subcortex for regions modulating nystagmus responses. Such areas might then be examined for collateral effects on behavior, mentation, and the like.

Consistent, apparently inhibitory responses were obtained from the mesencephalic tegmentum (brain-stem reticular core) and its rostral projections through the zona incerta and lateral hypothalamus. Evaluation of these results suggested they were due to nonreciprocally increased tension in all extraocular muscles with the result that true facilitatory influx to all muscles simultaneously produced apparent suppression of the vestibuloocular reflex.

Stimulation of the nucleus of Darkschewitsch was unique in producing a true inhibition of all extraocular muscles with relaxation of the eyeball in the socket. There were no associated general somatic or autonomic effects as with tegmental stimulation.

Stimulation of the entire central core of thalamic reticular nuclei, a thin midline extension into the caudal hypothalamus, and the external medullary lamina produced augmentation of nystagmus. A small dorsolateral island just medial to the lateral geniculate had similar effects.

Stimulation of the entire head and body of the caudate increased the amplitude of nystagmus, as it did in the fornix, while surrounding white matter of internal capsule and corona was generally inhibitory.

Physiologic and behavioral consequences of stimulation and/or ablation of these areas were considered. Effects of caudatal stimulation in particular were of interest; two separate groups of effects were noted, depending on the nature and parameters of stimulation. Both sets of phenomena were reminiscent of certain patterns shown by schizophrenic children and suggested the need for further evaluation of subcortical responses.

REFERENCES

1. Angyal, A., and Blackman, N.: Arch. Neurol. & Psychiat. 44:611, 1940.
2. Angyal, A., and Blackman, N.: Am. J. Psychiat. 97:894, 1941.
3. Bender, L., and Helme, W. H.: Arch. Neurol. & Psychiat. 70:413, 1953.
4. Colbert, E., and Koegler, R.: The childhood schizophrenic in adolescence. Presented at the one hundred fourteenth annual meeting of the American Psychiatric Association, May 16, 1960.
5. Colbert, E., and Koegler, R.: J. Pediat. 53:219, 1958.
6. Colbert, E. G., Koegler, R. R., and Markham, C. H.: Arch. Gen. Psychiat. 1:600, 1959.
7. Szentagothai, J., and Schab, R.: Acta physiol. Acad. Sci. Hungaricae 9:89, 1956.
8. Lachman, J., Bergmann, F., and Monnier, M.: Am. J. Physiol. 193:328, 1958.
9. Russell, G., and Johnson, F.: Anat. Rec. 112:464, 1952.

10. Nauta, W., and Kuypers, H.: Some ascending pathways in the brainstem reticular formation. In Reticular Formation of the Brain, edited by H. Jasper. Boston, Little, Brown & Co., 1958.
11. Scheibel, M., and Scheibel, A.: Structural substrates for integrative patterns in the brain stem reticular core. In Reticular Formation of the Brain, edited by H. Jasper. Boston, Little, Brown & Co., 1958.
12. Brodal, A., and Rossi, G. F.: Arch. Neurol. & Psychiat. 74:68, 1955.
13. Magoun, H. W., and Rhines, R.: J. Neurophysiol. 9:165, 1946.
14. Dareschewitsch, L.: Neurol. Centralbl. 4:100, 1885.
15. Ramon y Cajal, S.: Histologie du système nerveux de l'homme & des vertèbres. Vol. II. Madrid, Instituto Ramón y Cajal, 1955.
16. Pompeiano, O., and Walberg, F.: J. Comp. Neurol. 108:465, 1957.
17. Peacock, S. M., Jr.: J. Neurophysiol. 17:144, 1954.
18. Forman, D., and Ward, J. W.: J. Neurophysiol. 20: 230, 1957.
19. Mettler, F. A., and Mettler, C. C.: Brain 65: 242, 1942.
20. Jacobsen, C.: J. Comp. Neurol. 52:271, 1931.
21. Jacobsen, C.: Comp. Psychol. Mongr. 13:1; 61, 1936.
22. Tower, S. S.: Brain 58:238, 1935.
23. Jasper, H.: Electroencephalog. & Clin. Neurophysiol. 1:405, 1949.
24. Sharpless, S., and Jasper, H.: Brain 79:655, 1956.
25. Rothballer, A.: Studies on the adrenalin sensitive component of the reticular activating system. Thesis, McGill University, 1955.
26. Lorente de No, R.: Arch. Neurol. & Psychiat. 30: 245, 1933.
27. Rose, J. E., and Woolsey, C. N.: Electroencephalog. & Clin. Neurophysiol. 1:391, 1949.
28. Clare, M. H., and Bishop, G. H.: Electroencephalog. & Clin. Neurophysiol. 7:85, 1955.
29. Dempsey, E. W., and Morison, R. S.: Am. J. Physiol. 138:283, 1943.
30. Hunter, J., and Jasper, H.: Electroencephalog. & Clin. Neurophysiol. 1:305, 1949.
31. Hess, W. R.: Das Zwischenhirn. 2d ed., Basel, Schwabe, 1954.
32. Jasper, H., and Droogleever-Fortuyn, J.: Experimental studies on the functional anatomy of petit mal epilepsy. In Epilepsy, edited by W. G. Lennox, H. H. Merritt, and T. E. Bamford, Vol. XXVI, Research Publications, Association for Research in Nervous and Mental Disease. Baltimore, Williams & Wilkins, 1946, pp. 272-298.
33. Nashold, B. S., Hanbery, J. W., and Olszewski, J.: Electroencephalog. & Clin. Neurophysiol. 7:609, 1955.
34. Voneida, T. J.: Anat. Rec. 136:297, 1960.
35. Nauta, W., and Mehler, W.: Anat. Rec. 139:260, 1961.
36. Akert, K., and Andersson, B.: Acta physiol. scandinav. 22:281, 1951.
37. Heath, R. G., and Hodes, R.: Tr. Am. Neurol. A. 77:204, 1952.
38. Buchwald, N. A., and Ervin, F. R.: Electroencephalog. & Clin. Neurophysiol. 9:477, 1957.
39. Spiegel, E. A., and Szekely, E. G.: Arch. Neurol. 4:55, 1961.
40. Stevens, J. R., Kim, C., and MacLean, P. D.: Arch. Neurol. 4:47, 1961.
41. Gomez, J., Thompson, R., and Mettler, F.: Tr. Am. Neurol. A. 83:88, 1958.
42. Knott, J. R., Ingram, W. R., and Correll, R. E.: Arch. Neurol. 2:247, 1960.
43. Nothnagel, H.: Virchows Arch. path. Anat. 57: 184, 1873. Quoted by Jung and Hassler.[44]
44. Jung, R., and Hassler, R.: The extrapyramidal motor system. In Handbook of Physiology: Section I, Neurophysiology, edited by J. Field. Washington, D. C., American Physiological Society, 1959.
45. Ferrier, D.: West Riding Lunatic Asylum Med. Rep. 3:30, 1873. Quoted by Jung and Hassler.[44]
46. Vogt, C., and Vogt, O.: Heidelberg. Akad. Wissensch. Math. Natur. 14:3, 1919. Quoted by Stevens, Kim, and MacLean.[40]
47. Mettler, F., Hovde, C., and Grundfest, H.: Fed. Proc. 11:107, 1952.
48. Delmas-Marsalet, P., Bergouignan, M., and Verger, P.: Compt. rend. Soc. de biol. 118:1539; 119: 1219, 1935.
49. Scheibel, M., and Scheibel, A.: In Symposium on Hallucinations, edited by L. J. West. New York City, Grune & Stratton, in press, 1961.

Cryptococcic granuloma of the dorsal spinal cord

A case report

F. Miles Skultety, Ph.D., M.D.

INVOLVEMENT OF THE CENTRAL NERVOUS SYSTEM in Cryptococcus neoformans infections is well recorded in the literature. Such reports are no longer the rarity they once were; however, specific involvement of the spinal cord or its coverings with a granulomatous mass lesion is somewhat more rare. Carton and Mount[1] collected 9 cases from the literature and added 1 of their own in 1951. Only 5 of their 10 patients had such mass lesions. The present author has found records of 3 other reports of cryptococcic granulomatous lesions involving the spinal cord since that time.[2–4]

The following case report of a patient treated at the University Hospitals brings the total to 9.

CASE REPORT

First admission. H.F. (No. 60-500), a 60-year-old white insurance salesman, entered the University Hospitals for the first time on January 9, 1960. He gave a history of a fall on December 10, 1959, in which he landed on his buttocks. He fractured his left wrist, which was treated by the local doctor. At the time, he had many aches and pains including some pain of a rather diffuse character in his back and a sensation of numbness over the right lower abdomen and right anterior thigh. On December 24, he noticed frequency of urination, slight weakness of his legs on climbing stairs, and onset of severe pain radiating down the backs of both legs and originating in the region of the buttocks. The next day he had complete urinary retention requiring catheterization and was admitted to the local hospital. On December 28, at the time of transfer to another clinic, he was able to walk with support and had persistent, severe, radiating leg pain and a high fever. The pain subsided approximately one week after onset. Several days later, he was able to walk without support, and catheter drainage was no longer necessary by January 8. He was transferred to the University Hospitals on the next day.

Past history. The patient had a wedge resection of a granuloma in the lingula of the left lung on July 23, 1959. Because Ziehl-Nielson stains of the lesion revealed apparent acid-fast bacilli, the patient was treated with isoniazid and paraminosalicylic acid. He was discharged approximately one week after operation. Cryptococcus neoformans was subsequently cultured from the primary lesion, and pathologic examination of the specimen demonstrated the organisms within the lesion (Figs. 1 and 2). Cultures for tubercle bacilli from sputum and lung tissue were negative. The patient remained asymptomatic without further treatment until the onset of the present illness.

Physical examination. The patient was a well-developed, well-nourished white man appearing about the stated age of 60. There was a well-healed thoracotomy scar on the left chest wall. The general physical examination was not remarkable otherwise. The neurologic examination failed to demonstrate any abnormalities of the cranial nerves. Reflexes in the upper extremities were equal and active, and there were no demonstrable muscle weaknesses or sensory deficits. Examination of the lower extremities revealed slightly hyperactive and equal knee jerks and ankle jerks without

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clonus. Plantar stimulation elicited equivocal responses bilaterally. An area of hypalgesia and hypesthesia was demonstrable involving the right lower extremity and extending up onto the trunk to the D7 level with sacral sparing of segments 3, 4, and 5. There was no demonstrable sensory deficit on the left except for vibratory sense which was decreased up to the hips bilaterally, the right somewhat more so than the left. Position sense was intact in the toes. No muscle weakness was demonstrable about the toes or ankles; however, there was definite weakness of the more proximal musculature, the left somewhat greater than the right. The abdominal reflexes were absent. The right cremasteric was present, and the left was absent. When the patient walked, he had a somewhat waddling gait.

Course in hospital. Roentgenograms of the dorsal spine were negative except for mild degenerative arthritis. A chest plate showed the postoperative thoracotomy but no evidence of disease. A lumbar puncture performed at the time of myelography on January 12 revealed an initial pressure of 120 with a free rise and fall on jugular compression. Subsequent laboratory studies revealed no cells in the spinal fluid and a total protein of 266 mg. per cent. The contrast material could be carried to the cervical region without evidence of block, and the films were considered to be within normal limits.

The day after myelography, the patient stated that his legs seemed a little weaker, but no remarkable change could be found on repeat neurologic examination. During the evening of January 14, however, he had to be catheterized because he could not void. In the early morning hours the next day, he attempted to get out of bed and collapsed on the floor. Examination at that time revealed the strength of the patient's legs to be markedly decreased, and by the next morning he had only the ability to wiggle his toes. Sensory examination remained unchanged. The myelogram films were reviewed, and some stringy deformity of the dye column was noted about the region of the D6 body. The question was raised as to whether this indicated a vascular anomaly.

Operation. A laminectomy of D5, 6, and 7 was undertaken on January 16 under general anesthesia. When the dura was opened, the arachnoid appeared somewhat thickened and a bit more adherent to the cord than is usual. A mass approximately 1 × 1.5 cm. in size was found on the right dorsolateral surface of the cord at the region of the D6 vertebral body. It was quite hard to palpation and at first was felt to be separate from the cord; however, subsequent examination revealed that it arose from the cord. A biopsy was taken and frozen section examination carried out. This was reported to be consistent with a granuloma. Just

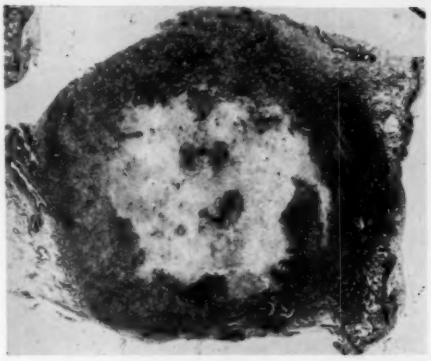

Fig. 1. Cross section of lesion removed from lingula of left lung

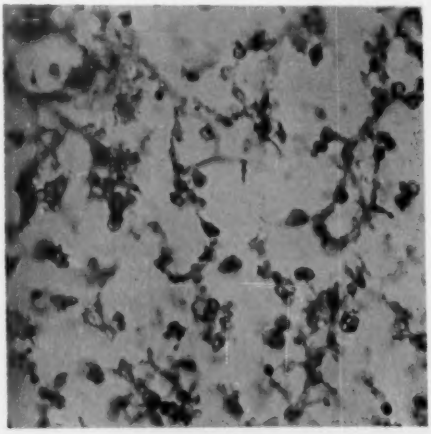

Fig. 2. Photomicrograph from lung lesion showing cryptococcic organisms. Periodic Acid-Schiff stain. × 600

rostral to this area, the cord appeared somewhat swollen. It was split in the midline dorsally, and, at a depth of approximately 1½ mm., a slightly grayish, hard mass was encountered. This seemed to be readily separable from the cord substance, and the mass was gently freed. As the rostral pole of the mass was being freed, purulent material escaped from beneath it. A culture was taken of this material. Although the rostral pole could be freed, the mass was not separable from the cord caudally and seemed to fan out diffusely in the direction of the previously described dorsolateral excrescence. It became obvious at this point that total excision of the mass, or masses, could not be carried out without considerable damage to the cord. That portion of the intramedullary mass which was free was resected, and the operation was terminated in a routine manner.

Postoperative course. Postoperatively, the patient was unable to move his lower extremities. There was analgesia and anesthesia up to the D7 dermatome on the right and some hypalgesia in the lower extremity, with a band of hypalgesia in the region of the D7 dermatome on the left. Sacral sparing was still present. Vibratory sense was absent bilaterally below and including the iliac crest. Position sense was absent in the toes. During the rest of this admission, the patient's neurologic status remained essentially unchanged except that analgesia and anesthesia gradually developed on the left side and the sacral sparing disappeared.

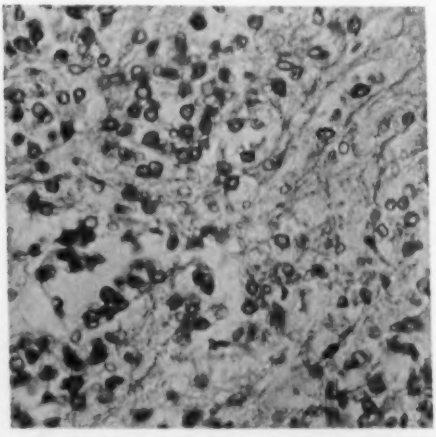

Fig. 3. Photomicrograph of material removed from dorsal cord at surgery. Note numerous organisms throughout section. Alcian blue stain. × 600

The culture taken at the time of operation grew Cryptococcus neoformans. Permanent sections of the specimen removed revealed it to be a granuloma, and cryptococcic organisms were demonstrated (Fig 3). A course of amphoteracin B was started on January 21. An initial dose of 0.25 mg. per kilogram of body weight was used and this was gradually increased to a total of 1.5 mg. per kilogram. The drug was given intravenously slowly over a period of five to six hours each day. The patient experienced some chills and fever with vomiting, apparently secondary to the drug. The patient's blood urea nitrogen, white count, and peripheral smear were followed closely. On February 9, blood urea nitrogen rose to 55 mg. per cent, and amphoteracin B was discontinued at a total accumulated dose of 1.6 gm.; 3 cultures of spinal fluid taken February 1, 4, and 7 were negative for Cryptococcus neoformans.

The patient remained fever-free without generalized evidence of infection up to the time of his discharge on February 17, 1960, when he was transferred to a local hospital.

Second admission. The patient was readmitted to the University Hospitals on August 31, 1960. He had received physiotherapy locally and was ambulating somewhat with crutches and long leg braces.

Physical examination. The patient had furuncles on his left hand and right leg and a papular, pustular rash in both groins. He could move his toes and dorsiflex both feet on command. Some hypalgesia and hypesthesia of the right leg and trunk up through the D9 dermatome were noted.

Course. Lumbar puncture revealed 32 lymphocytes per cubic millimeter, a total protein of 650 mg. per cent, and a sugar of 18 mg. per cent. A culture taken of the fluid was negative for bacteria, yeast, and fungi. The patient had a generalized furunculosis which, upon culture, grew Staphylococcus aureus. Despite antibiotics, this did not come under control. He became confused and progressively more lethargic and finally died on September 16, 1960.

Postmortem findings. Examination revealed generalized furunculosis and bilateral pneumonia with more severe involvement of the left lung. The lesions in the left lung were felt to be consistent with cryptococcosis, but examination failed to reveal the presence of the organisms. Culture of the blood and spinal fluid at autopsy were negative for bacteria, yeast, and fungi. Examination of the brain revealed generalized thickening of the arachnoid over the convexities and the base but no grossly purulent material. When the brain was sectioned, the ventricles were found to be involved with an ependymitis, and a thick gelatinous exudate was present in the left lateral ventricle. Histologic examination of this ventricular wall revealed cryptococcic organisms within the inflammatory lesion. Examination of the spinal cord revealed an inflammatory lesion still present at the D6 level and multiple granulomatous lesions scattered among the cauda equina.

DISCUSSION

Only 8 cases of actual involvement of the spinal cord or the cauda equina with a granulomatous mass lesion of cryptococcus origin were found among those reported in the literature. Other cases reported as cryptococcosis of the spinal cord turned out to be meningitis with perivascular infiltration or myelitis. This was true of 5 of the 10 cases reported by Carton and Mount[1] as well as the case of Jones and Klinck[5] referred to by Ley, Jacas, and Oliveras.[3] In the author's attempt to find further reports of cryptococcosis of the spinal cord, numerous other similar reports were encountered.

In the 8 cases mentioned above, the lesions were discovered at postmortem examination in 3 instances.[6–8] Laminectomies were performed in the remaining 5 cases; however, in the case of Goodhart and Davison,[9] no lesion was found at either of 2 laminectomies. The patient subsequently died of cryptococcic meningitis, and a granulomatous collection in the cord with thickened meninges was found at the D10 level at postmortem examination.

The case of Carton and Mount[1] represents the first reported laminectomy, performed because of symptoms due to a mass lesion, in which a granuloma was actually encountered at surgery. The mass, involving the cauda equina, was not totally excised. The patient

SURGICAL INTERVENTION IN CRYPTOCOCCOSIS OF THE SPINAL CORD

Author	*Date of operation*	*Spinal cord pathology*	*Results*
Goodhart and Davison[9]	?/?/33	Demyelinization at D10. Granulomatous collections throughout cord at autopsy	Both explorations negative. Patient later had meningitis and died 1/6/35.
Carton and Mount[1]	4/24/47	Intradural granulomatous mass involving cauda equina D12 to L4	Not removed. All postoperative cultures negative except one. Patient paraplegic but without further central nervous system involvement 31 months later
Ley, Jacas, and Oliveras[3]	11/7/49	Intradural, extramedullary granuloma. Upper end in cisterna magna, lower end 2 cm. above lower end of cervical canal	Mass removed en bloc. No postoperative cultures reported. Patient completely recovered 8 months after operation
Ramamurthi and Anguli[4]	1/16/53	Intramedullary granuloma ⅝ x ⅝ in. in cord at D2 vertebral level	Mass removed. No culture reported. Patient recovered except for right leg weakness 1 year later
Alajouanine, Houdart, and Drouhet[2]	1/22/53	Intradural granulomatous mass involving cauda equina L2 to L5	Not removed. Treated with drugs. 7 negative cultures. No neurologic improvement in 8 weeks
Skultety	1/16/60	Intramedullary granuloma in cord at D6 vertebral level	Not removed. Treated with amphoteracin B. Minimal temporary improvement. Patient died 9 months later.

was alive thirty-one months after surgery, paraplegic but without further evidence of central nervous system involvement. Alajouanine, Houdart, and Drouhet[2] recorded a laminectomy on a 53-year-old woman with an inoperable granulomatous mass involving the cauda equina. Subsequent treatment with numerous medical agents was carried out, but only an eight-week follow-up was reported.

The report by Ley and associates[3] in 1951 represents the first recorded case of actual removal of the lesion. This was an intradural, extramedullary lesion lying posterior to the cervical cord. The patient was seen eight months later with complete recovery and no further central nervous system involvement.

In November 1954, Ramamurthi and Anguli[4] first reported the successful removal of an intramedullary granuloma at the D2 vertebral level in a 17-year-old girl. Examination one year later revealed recovery with some remaining weakness of the right leg.

The case reported in this paper brings the total of surgical interventions to 6 and is unique among the cases cited in the fact that the patient had undergone a previous resection of a pulmonary cryptococcic lesion. White and Arany[10] reviewed 26 cases of localized pulmonary cryptococcosis treated by resection. They pointed out that, in 17% of these recorded cases, no previous central nervous system involvement was found but did develop subsequently. In none of these, however, was a subsequent neurosurgical procedure reported to have been carried out. The 6 cases discussed in the present paper are summarized in the table.

SUMMARY

A case of involvement of the spinal cord with a cryptococcic granuloma is reported in a patient who had previously had a similar granuloma resected from the lung. The lesion was intramedullary in the dorsal region and could not be totally resected. The reports of 5 previous attempts at neurosurgical intervention including 2 successful removals are cited and discussed.

The author would like to thank Dr. R. B. Rasmus of the Gunderson Clinic, La Crosse, Wis., for making available to him a summary of the patient's previous hospitalization and operative procedure on the lung. He would also like to thank Dr. James L. Jaeck, pathologist at the Lutheran Hospital, La Crosse, for making available the slides of the lung lesion and for his permission to reproduce photographs of those slides.

REFERENCES

1. Carton, C. A., and Mount, L. A.: Neurosurgical aspects of cryptococcosis. J. Neurosurg. 8:143, 1951.
2. Alajouanine, T., Houdart, R., and Drouhet, E.: Les formes chirurgicales spinales de la torulose; torulome de la queue de cheval. Rev. neurol. 88:153, 1953.
3. Ley, A., Jacas, R., and Oliveras, C.: Torula granuloma of the cervical spinal cord. J. Neurosurg. 8:327, 1951.
4. Ramamurthi, B., and Anguli, V. C.: Intramedullary cryptococcic granuloma of the spinal cord. J. Neurosurg. 11:622, 1954.
5. Jones, S. H., and Klinck, G. H., Jr.: Torula histolytica (Cryptococcosis hominis) meningitis: Case report and therapeutic experiments. Ann. Int. Med. 22:736, 1945.
6. Fitchett, M. S., and Weidman, F. D.: Generalized torulosis associated with Hodgkin's disease. Arch. Path. 18:225, 1934.
7. Reeves, D. L., Butt, E. M., and Hammack, R. W.: Torula infection of the lungs and central nervous system. Arch. Int. Med. 68:57, 1941.
8. Smith, F. B., and Crawford, J. S.: Fatal granulomatosis of the central nervous system due to a yeast (torula). J. Path. & Bact. 33:291, 1930.
9. Goodhart, S. P., and Davison, C.: Torula infection of the central nervous system. Arch. Neurol. & Psychiat. 37:435, 1937.
10. White, M., and Arany, L. S.: Resection in pulmonary cryptococcosis (torulosis). J. Thoracic Surg. 35:402, 1958.

Studies of cerebrospinal fluid proteins precipitated by zinc sulfate solutions

W. K. Hass, M.D., and G. M. Hochwald, M.D.

IMMUNOCHEMICAL, paper electrophoretic, and agar gel electrophoretic methods have conclusively demonstrated elevations in the gamma globulin fraction of the cerebrospinal fluids of a large percentage of patients with multiple sclerosis, neurosyphilis, and certain "inflammatory" diseases of the central nervous system.[1–4] These methods, however, require for their performance either special facilities beyond the scope of a routine clinical laboratory or a large volume of cerebrospinal fluid for concentration. As a result, there has been a continuing interest in methods which employ a heavy metal protein precipitin ($ZnSO_4 \cdot 7H_2O$) in a barbiturate buffer with or without added ethanol.[5,6]

This interest has largely stemmed from the observations of Roboz, Hess, and Forster[6] on the nature of the proteins precipitated by zinc sulfate and ethanol from a large volume of concentrated cerebrospinal fluid. Using a Tiselius apparatus and paper electrophoresis, these workers found only one protein component in the precipitate, which was gamma globulin. This observation was reinforced by the quantitative recovery of gamma globulin from the cerebrospinal fluid after addition of measured amounts of pure gamma globulin. Later investigators have offered modifications of this technic, identifying their precipitates also as gamma globulin.[7–9]

In the attempt to study neurologic syndromes characterized by elevated cerebrospinal fluid gamma globulin with the zinc precipitin technic, we found unexpectedly variable results. To explain this variation, washed and unwashed precipitates were studied by the recently developed and highly sensitive immunoelectrophoretic technic.[10] This method allows the sampling of very small amounts of precipitate and reveals more than one protein species in the precipitates as the gamma globulin fraction increases.

METHOD

The following two solutions were employed for protein precipitation.

Solution 1: Zinc sulfate ($ZnSO_4 \cdot 7H_2O$) in a barbital buffer adjusted to *p*H 7.3 with sodium hydroxide. This contained 1.45 gm. of zinc sulfate, 3.60 gm. of barbital, and 1.50 gm. of sodium barbital in 1 liter of demineralized water. This is the solution described by Papadopoulos and associates.[8]

Solution 2: The above mixture to which 95% ethanol was added to 10% of the total volume. This solution was used by Roboz and associates[6] and Hanok.[9]

Samples of cerebrospinal fluid, 1 or 2 cc., were pipetted into stoppered centrifuge tubes. An equal volume of chilled solution 1 or 2 was added to the fluid. The tubes were agitated initially and after ten minutes, then placed in the refrigerator overnight. After centrifugation for five minutes, the supernatant was poured off and the precipitate was either studied as such or washed one to four times with the cold solution used for precipitation diluted with an equal volume of cold demineralized water.

The washed and unwashed precipitates were redissolved in 0.1 cc. of a 22-millimole solution of disodium ethylenediaminetetraacetic acid (EDTA). Paired samples were resuspended in a 1.25% sodium carbonate solution for protein determination using Folin-Ciocalteu reagent diluted 1 to 3.

A modification of Scheidegger's technic[11] for agar gel immunoelectrophoresis was employed. Agar in a barbital buffer of *p*H 8.6, ionic

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Fig. 1. Immunoelectrophoretic patterns of zinc-alcohol protein precipitates from cerebrospinal fluid of patient with encephalopathy of unknown cause, row 1-3. Pattern of normal concentrated cerebrospinal fluid is shown in row 4.

strength 0.075, was poured on 3¼ by 4 in. lantern slides. In all experiments, approximately 10 microliters of the redissolved precipitate in EDTA solution containing 1 to 50 μg. of protein was placed in the antigen wells. A rabbit antiserum prepared against normal human serum was placed in the troughs after electrophoresis of the redissolved precipitates. The low antigen concentration made it necessary to dilute the antisera three to five times in order to obtain sharp precipitin lines.

After washing, the slides were dried and stained with amido black 10B by the method of Uriel and Scheidegger.[12] By this method, as little as 3 μg. of precipitate could be resolved as a faint line.

A Versatol* protein standard containing 19% gamma globulin by electrophoresis diluted to 69 to 80 mg. per cent protein in 0.9% saline was used to study the effect of addition of albumin to a solution resembling cerebrospinal fluid but richer in gamma globulin than normal cerebrospinal fluid.

*Versatol is a blood chemistry standard containing dialyzed dried human serum and was supplied by Warner-Chilcott Laboratories, Morris Plain, N. J.

RESULTS

The nature of the precipitate from a cerebrospinal fluid typical of those with an increase in the gamma globulin fraction is presented in Figure 1. The fluid was from a patient with encephalopathy of unknown cause. The total protein was 126 mg. per cent. The twice-washed precipitates after treatment with solution 1 or 2 contained 37% of the total protein. In Figure 1, the precipitate from solution 2 is presented, washed once in row 1, twice in row 2, and three times in row 3. For comparison, a normal concentrated cerebrospinal fluid—not a precipitate—is presented in row 4. Regardless of the number of washings, the precipitate contained, in addition to gamma globulin, a significant amount of albumin and small amounts of alpha$_1$ and alpha$_2$ globulins. The patterns presented by precipitates obtained by the use of solution 1 in this case were similar to those pictured. Increased numbers of washings resulted in slight progressive diminution of all the protein components.

In contrast, cerebrospinal fluids from patients with nondemyelinating and noninflammatory diseases of the central nervous system yielded very small precipitates with protein values similar to those previously reported for the method, 2 to 4 mg. per cent. By our technic, 10-microliter samples of redissolved precipitates of this magnitude contained only 2 to 4 μg. of protein. Concentrations of this order yielded at best faint albumin lines from unwashed precipitates. Often, no lines were seen after precipitates were washed (Fig. 2, row 2).

It was therefore of interest to study the effect of the addition of increasing amounts of pure gamma globulin* to such a cerebrospinal fluid. Immunoelectrophoretically pure (Fig. 2, row 1) human serum gamma globulin was added to the cerebrospinal fluid of a patient with hypertensive vascular disease. The

*Fraction II, 1,2. Run 1068. Protein Foundation Laboratories, Jamaica Plains, Boston, Mass.

total protein content was 65 mg. per cent. The procedure is outlined in Table 1.

The addition of gamma globulin results in an initial sharp increase in the amount of precipitate, which was 3 times as great as the amount of added gamma globulin. Immunoelectrophoresis of this redissolved precipitate reveals a well-defined albumin line and a less distinct gamma globulin line (Fig. 2, row 3). Larger amounts of added gamma globulin result in an increase in total precipitate. Although the increase in precipitate approaches the amount of gamma globulin added, this increase does not represent only the added gamma globulin, since there is an increased density of the albumin lines associated with the increased density and length of the gamma globulin precipitin lines (Fig. 2, rows 4 and 5). This increase in albumin suggests that it is a coprecipitin under these circumstances. The similarity of these precipitates to those from abnormal cerebrospinal fluids (Fig. 1) suggests that albumin in those fluids plays a similar role.

Regardless of the nature of the precipitate, it is apparent that small increases in the gamma globulin fraction are responsible for sharp increases in zinc turbidity. Small increases in the albumin* fraction, on the other hand, have no effect on the total quantity of precipitate or on its immunoelectrophoretic character. When the amount of added albumin exceeds the total protein concentration, however, small increases in the total amount of precipitate occur, paralleled by increases in the density of the albumin line (Table 2, Fig. 3).

*Normal serum albumin, human salt poor, USP. Lot No. 490F11. Hyland Laboratories, Los Angeles.

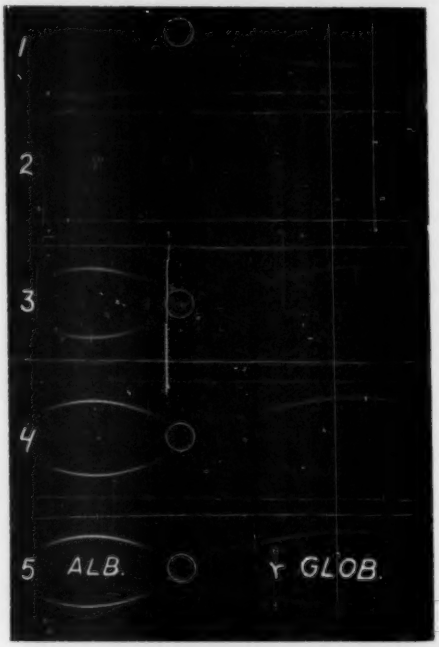

Fig. 2. Immunoelectrophoretic pattern of pure gamma globulin, row 1; of small precipitate from cerebrospinal fluid of patient with hypertensive vascular disease, row 2; and of precipitates from same fluid after addition of increasing amounts of gamma globulin, rows 3-5

DISCUSSION

In 1947, Kunkel[13] demonstrated that addition of specific concentrations of copper or zinc sulfate to sixtyfold dilutions of serum caused turbidities in abnormal sera which

TABLE 1
EFFECT OF ADDITION OF GAMMA GLOBULIN TO CEREBROSPINAL FLUID

Amount of fluid (cc.)	*Amount of solution 2 (cc.)*	*Added gamma globulin (microliters)*	*Estimated concentration of added gamma globulin (mg. per cent)*	*Concentration of protein in precipitate (mg. per cent)*	*Immunoelectrophoretic pattern*
1	1	0	0	2	Figure 2, row 2
1	1	10	5	19.5	Figure 2, row 3
1	1	25	12.5	26	Figure 2, row 4
1	1	50	25	37	Figure 2, row 5

TABLE 2
EFFECT OF ADDED ALBUMIN

Amount of Versatol solution, protein concentration 80 mg. per cent (cc.)	*Amount of solution 2 (cc.)*	*Added albumin (microliters)*	*Estimated concentration of added albumin (mg. per cent)*	*Concentration of protein in precipitate (mg. per cent)*	*Immunoelectrophoretic pattern*
1	1	0	0	12	Figure 3, row 1
1	1	5	10	12	Figure 3, row 2
1	1	10	20	12	Figure 3, row 3
1	1	50	100	13.5	Figure 3, row 4
1	1	100	200	16	Figure 3, row 5

appeared to correlate well with increases in the gamma globulin fraction. Electrophoretic studies of the copper sulfate precipitates of four sera revealed that the chief protein component was gamma globulin. Lesser amounts of other proteins including albumin were also noted.

Fig. 3. Immunoelectrophoretic pattern of zinc-alcohol protein precipitates from dilute Versatol solution showing effect of increasing amounts of albumin

The simplicity of Kunkel's technic prompted Donovan, Foley, and Moloney[5] to apply it to the study of globulin abnormalities in the cerebrospinal fluid. Using zinc sulfate in a barbital buffer—essentially solution 1 not adjusted to *p*H 7.3—these investigators found 2 to 4+ precipitin reactions in more than 90% of patients with neurosyphilis and 2 to 3+ precipitin reactions in more than 90% of patients with multiple sclerosis. By contrast, only 17% of patients with vascular disease and less than 10% of patients with miscellaneous illnesses exhibited a precipitin reaction, usually 1 to 2+ in character.

Roboz, Hess, and Forster[6] found that the amount of precipitate could be increased by the adjustment of *p*H to 7.3 and the addition of 95% alcohol to the zinc-barbital solution of Donovan. By their method, they achieved quantitative recovery of 100- to 500 μg. amounts of gamma globulin added to 5-cc. aliquots of cerebrospinal fluid. It is important to note, however, that these precipitates were not studied electrophoretically. It was not established directly, therefore, that the increased precipitate consisted only of gamma globulin. Our similar experiments (Table 1, Fig. 2) have shown that low concentrations of added gamma globulin cause an initial sharp rise in the protein content of the precipitate in excess of added globulin. Larger additions result in increases in the amount of precipitated protein which parallel the level of added globulin. The increased precipitate, however, is due to increases in not one but many protein species.

Applying their method to the study of cerebrospinal fluids of patients with multiple sclerosis, Roboz, Hess, and Forster found an average value of 12.6 mg. per cent of "gamma

globulin" representing an average of 22% of the total protein. In contrast, patients with nondemyelinating disease averaged 2 mg. per cent gamma globulin, representing an average of 4.5% of the total protein. Later paper electrophoretic studies by the same investigators[14] showed an average value of 35.9% gamma globulin in the cerebrospinal fluids of patients with multiple sclerosis against a normal value of 16.5%. This discrepancy of 61% in patients with multiple sclerosis and 300% in normal persons confirms the fact that proteins are incompletely precipited by the zinc precipitin method. It can be concluded that the zinc precipitin technic has diagnostic value if a consistent correlation can be made between the presence of marked turbidity and the existence of demyelinating or inflammatory disease of the central nervous system. It should be emphasized, however, that the precipitates from such spinal fluids contain proteins other than gamma globulin. The technic should, therefore, be regarded as a zinc or zinc-ethanol precipitin method rather than as an accurate gamma globulin determination. Where the latter is required, the more specific precipitin technic of Kabat is indicated.

SUMMARY

Precipitates of proteins from cerebrospinal fluids prepared by the addition of zinc sulfate in a barbital buffer and ethanol were studied by the technic of immunoelectrophoresis. Though the amount of precipitate increased as the proportion of gamma globulin increased, it was found that precipitates from abnormal cerebrospinal fluids contained a mixture of proteins and not solely gamma globulin. When used in the study of demyelinating diseases and neurosyphilis, this method of cerebrospinal fluid protein estimation should be described as a zinc precipitin technic and not as a gamma globulin determination.

The authors would like to thank Drs. G. J. Thorbecke and R. Asofsky for their kind help and suggestions.

REFERENCES

1. Kabat, E. A., Glusman, M., and Knaub, V.: Quantitative estimation of the albumin and gamma globulin in normal and pathologic cerebrospinal fluid by immunochemical methods. Am. J. Med. 4:653, 1948.
2. Yahr, M. D., Goldensohn, S. S., and Kabat, E. A.: Further studies on gamma globulin content of cerebrospinal fluid in multiple sclerosis and other neurological diseases. Ann. N. Y. Acad. Sc. 58:613, 1954.
3. Ivers, R. R., McKenzie, B. F., McGuckin, W. F., and Goldstein, N. P.: Spinal-fluid gamma globulin in multiple sclerosis and other neurologic diseases. J.A.M.A. 176:515, 1961.
4. Lowenthal, A., van Sande, M., and Karcher, D.: The differential diagnosis of neurological diseases by fractionating electrophoretically the CSF γ-globulins. J. Neurochem. 6:51, 1960.
5. Donovan, A. M., Foley, J. M., and Moloney, W. C.: The precipitation of cerebrospinal fluid globulin by zinc sulfate. J. Lab. & Clin. Med. 37:374, 1951.
6. Roboz, E., Hess, W. C., and Forster, F. M.: Quantitative determination of gamma globulin in cerebrospinal fluid. Neurology 3:410, 1953.
7. Ziegler, D. K., and Ross, G.: Cerebrospinal fluid gamma globulin as a diagnostic test for multiple sclerosis. Neurology 5:573, 1955.
8. Papadopoulos, N. M., Hess, W. C., O'Doherty, D. O., and McLane, J. E.: A procedure for the determination of cerebrospinal fluid total protein and gamma globulin in neurologic disorders. Clin. Chem. 5:569, 1959.
9. Hanok, A.: A micro modification of a method for the measurement of globulin in cerebrospinal fluid and its application in diagnosis of multiple sclerosis. J. Lab. & Clin. Med. 57:42, 1961.
10. Grabar, P., and Williams, C. A.: Méthode permittant l'étude conjuguée des propriétés électrophorétiques et immunochemiques d'un mélanges de protéines. Biochim. et biophys. acta 10:193, 1953.
11. Scheidegger, J. J.: Une micro-méthode de l'immunoélectrophorèse. Internat. Arch. Allergy 7:103, 1955.
12. Uriel, J., and Scheidegger, J. J.: Électrophorèse en gélose et coloration des constituants. Bull. Soc. chim. biol. 37:165, 1955.
13. Kunkel, H. G.: Estimation of alteration of serum gamma globulin by a turbidimetric technique. Proc. Soc. Exper. Biol. & Med. 66:217, 1947.
14. Roboz, E., Hess, W. C., Forster, F. M., and Temple, D. M.: Paper electrophoretic studies in multiple sclerosis. Neurology 4:811, 1954.

Intracranial calcification and hypoparathyroidism

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INTRACRANIAL CALCIFICATION may conveniently be classified into two categories: the physiologic and the pathologic. Physiologic calcification is often found in the following structures: the choroid plexus, pineal body, habenula, falx cerebri, pterygoclinoid ligaments, and arachnoid granulations. Pathologic intracranial calcification is seen in toxoplasmosis, cysticercosis, trichinosis, brain abscess, tuberculosis, tuberous sclerosis, arteriosclerosis, angiomas, aneurysms, hematomas, brain tumors, and hypoparathyroidism. Occasionally, intracranial calcification is associated with microcephaly and other cerebral dysmorphias.

It is the purpose of this paper to draw attention to the occurrence of intracranial calcification in hypoparathyroidism by illustrative case reports and a brief review of the literature.

CASE REPORTS

Case 1. A. B., a 30-year-old white man, was first seen in 1949 for evaluation of right-sided seizures which started at the age of 13. A typical seizure began with weakness in the right lower limb, followed rapidly by the appearance of muscle spasm with inversion and plantar flexion of the foot. At the same time, the muscles of the right side of the face would contract. The attacks lasted only a few seconds and were not associated with impairment of consciousness, tongue biting, or incontinence. Speech was difficult during an attack, but the patient stated that this was due to spasm of the facial muscles. At first, the attacks occurred twice a day, precipitated by any sudden action. They then occurred at irregular intervals with the longest period of freedom from attack being two weeks.

The significant past history included measles during childhood associated with loss of vision for a few weeks, followed by gradual recovery.

On physical examination, the patient was well developed; vital signs were within normal limits. Ophthalmologic examination revealed small lenticular opacities and disseminated areas of chorioretinitis. Whitish granulomatous lesions were noted at the corners of the mouth. The signs of Chvostek and Trousseau were absent. Neurologic examination was within normal limits; deep tendon reflexes were active.

The hemogram and urinalysis were within normal limits. Serology was negative. The nonprotein nitrogen was 42 mg. per cent; fasting blood sugar, 90 mg. per cent; and cerebrospinal fluid protein, 16 mg. per cent.

Skull roentgenograms (Fig. 1) revealed bilateral linear and flocculent areas of calcification lateral to the caudate nuclei, numerous small crescentic areas representing convolutional calcification, and a few finer areas of calcification in the cerebellum. The pineal body was not calcified. The bones of the skull showed no visible abnormality. Examination of the jaws showed numerous unerupted incisors and cuspids and several unerupted molars in the upper and lower jaws. On pneumoencephalographic study, there was no evidence of dilation or displacement of the ventricular system. Roentgenograms of the chest, abdomen, and kidneys (intravenous pyelogram) showed no abnormalities.

Skull films of the patient's parents and three siblings were normal.

The electroencephalogram showed a very regular alpha rhythm with interference by slower frequencies ranging from 2.5 to 5 per second. Forced hyperventilation produced minimal accentuation of the 4- to 5-per-second waves. An electrocardiogram was within normal limits save for a Q-T interval 30% above normal, suggesting hypocalcemia. However, the serum calcium determinations ranged between 8.7 and 12 mg. per cent, and concomitant serum phosphorus determinations ranged between

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This work was supported in part by Research Grant A-4340 from the National Institute of Arthritis and Metabolic Diseases.

4.5 and 5 mg. per cent. The serum alkaline phosphatase was 4 Bodansky units. Diphenylhydantoin was prescribed, and the patient was discharged.

Because of continuation of attacks and development of concentric constriction of vision, the patient was readmitted in 1959. Ophthalmologic examination confirmed the diagnosis of retinitis pigmentosa made ten years earlier. Constriction of the visual fields and loss of night vision were consistent with this diagnosis. Electroencephalographic examination was now within normal limits. Skull roentgenograms were unchanged from previous examinations. Monilia albicans was cultured from an area of whitish exudate over the palate; monilia was also cultured from the left thumb nail and the left index finger.

In order to elucidate the etiology of the convolutional calcification, a biopsy of the right frontal cortex and adjacent white matter was performed. Grossly, the tissue had a granular consistency. On microscopic section, heavy calcium deposits were present in the cortex (Fig. 2). Calcium deposits were present in the media and adventitia of arteries in the cerebral white matter (Fig. 3). Concretions were also noted to lie free in the white matter, while calcium stains revealed heavy calcification and pericapillary beading. Iron stains revealed almost no iron deposits. Holtzer stain for glial fibers revealed no gliosis.

Postoperatively, a wound infection developed, from which alpha streptococci were cultured. This was successfully treated with antibiotics. During the height of the infection, there was marked generalized neuromuscular irritability and a positive Chvostek sign. After the application of a tourniquet to the right arm, sweating, numbness of the right leg, and clonic movements of the right leg and arm, neck, and face occurred. Clonic movements of the right extremities lasted for one minute; the patient was fully conscious during this time. Calcium chloride was administered intravenously, and the patient felt more relaxed. The serum calcium drawn during the seizure was reported as 4.3 mg. per cent, and the serum phosphorus was 6 mg. per cent. Treatment with calcium gluconate and vitamin D_2 was instituted with restoration of serum calcium and phosphorus concentrations to normal. A clinical diagnosis of hypoparathyroidism was made, and the patient was discharged on vitamin D_2, 50,000 units twice a week.

In March 1960, the patient was readmitted for periodic reevaluation. Serum calcium was 8.5 mg. per cent and phosphorus, 4.3 mg. per cent. The serum albumin was 3.9 gm. per cent and globulin, 3.4 gm. per cent. The plasma protein electrophoretic pattern was normal. The protein-bound iodine was 4.4 μg. per cent. Twenty-four-hour urinary excretion of 17-ketosteroids was 24 mg. The patient was continued on vitamin D_2; no further seizures occurred.

He was readmitted in February 1961 for acrylic cranioplasty and further studies of his calcium

Fig. 1. *(Case 1)* Lateral skull film. Marked convolutional, basal ganglia, and cerebellar calcification

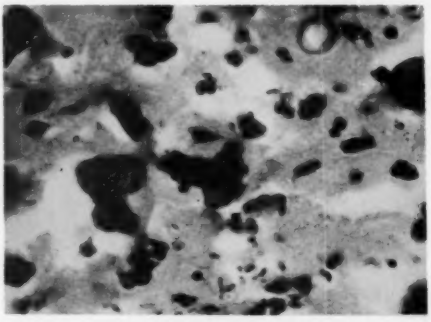

Fig. 2. *(Case 1)* Cerebral cortex. Heavy calcium deposits in form of concretions lie free in gray matter. Hematoxylin and eosin stain. × 400

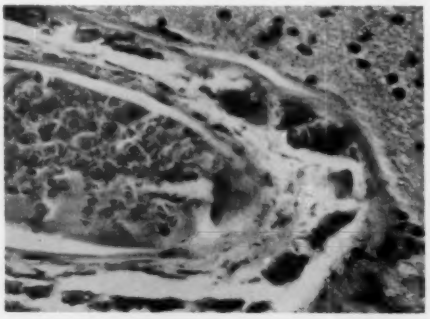

Fig. 3. *(Case 1)* Artery in subcortical white matter. Concrements of calcium are seen in media of vessel. Hematoxylin and eosin stain. × 400

metabolism on maintenance vitamin D_2 therapy. The phosphate reabsorption index was 0.93 before and 0.91 after an intravenous calcium infusion (15 mg. of calcium ion per kilogram in 1000 cc. of normal saline over a four-hour period). The phosphate clearance was 6.2 cc. per minute before infusion and 7.4 cc. per minute eight hours after infusion. The twenty-four-hour urinary phosphate excretion rose from 514 mg. before infusion to 814 mg. during the twenty-four hours following infusion. The serum phosphorus rose from 3.4 mg. per cent just before infusion to 5.1 mg. per cent immediately afterward. The high phosphate reabsorption index, low clearance of phosphate before and after calcium infusion, and increase in total urinary phosphate excreted after calcium infusion were consistent with the diagnosis of hypoparathyroidism.

Case 2. D. R., a 35-year-old white woman, was hospitalized in January 1959 for evaluation of headache. Headaches first occurred in 1947, apparently related to domestic difficulties and accompanied by crying spells, syncope, and bilateral occipitofrontal pain. The patient described both sharp and dull components to these headaches. They were increased by emotion and were not relieved by aspirin but were ameliorated by rest.

The past history revealed that she had sustained a head injury with brief unconsciousness in 1944. Skull roentgenograms were not taken at that time. In January 1956, she underwent a radical hysterectomy for stage I carcinoma of the cervix. She experienced hot flashes after surgery; no hormonal therapy was given.

On physical examination, the patient was a well-developed, stocky woman; she was oriented and cooperative. Vital signs were within normal limits. There was no evidence of ectodermal defects, metacarpal shortening, cataracts, or chronic monilial infection of the mouth or nails. Her face was not abnormally round. Examination of the fundi, motor and sensory modalities, and reflexes was normal; there was no rigidity, tremor, or dysmetria. The signs of Chvostek, Trousseau, and Lust were not elicited. Hyperventilation did not produce signs of tetany. On pelvic examination, no evidence of recurrent tumor was noted. Several dental caries were noted on full-mouth roentgenograms; there was no hypoplasia or blunting of the molar roots.

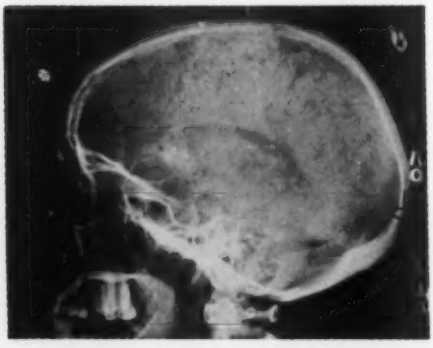

Fig. 4. *(Case 2)* Lateral projection of pneumoencephalogram demonstrating calcification adjacent to anterior horn of lateral ventricle

Roentgenographic examination of the skull revealed bilateral symmetric areas of calcification in the region above the sella turcica approximately one-third of the distance from the anterior clinoid processes to the vertex of the skull. In the right lateral projection, the area of calcification was ovoid in shape and measured 2.3 × 1 cm. The posterior-anterior projection demonstrated areas of calcification measuring 1 cm. in diameter. The pneumoencephalographic study (Fig. 4) demonstrated these areas of calcification to be in contact with the anterior horns of the lateral ventricles. There was no shift in the ventricular system. It was concluded from the study that the calcification was present in the basal ganglia, primarily in the region of the head of the caudate nuclei.

Urinalysis and hemogram were within normal limits. Serology was negative. On spinal fluid examination, there were 2 red blood cells per cubic millimeter and a protein of 13 mg. per 100 cc. The blood urea nitrogen was 16 mg. per cent. The serum albumin was 4.9 gm. per cent, and the serum globulin was 2.6 gm. per cent. The laboratory values for serum calcium during hospitalization were 9.2, 7.5, 10.0, and 9.6 mg. per cent. Serum phosphorus values on corresponding occasions were 7.9, 4.8, 4.3, and 4.2 mg. per cent.

The resting electroencephalogram demonstrated no abnormalities. Two minutes after hyperventilation, generalized bursts of nonspecific, high-voltage, 5- to 6-per-second waves developed which persisted fifteen to twenty seconds after hyperventilation ceased; 600 mg. of calcium gluconate were given intravenously during repeated hyperventilation with no essential change in the electroencephalogram.

In order to determine if hypoparathyroidism was present, the intravenous calcium-loading test was performed. The patient was placed on a constant calcium and phosphorus (Bauer-Aub) diet; 2 twenty-four-hour specimens collected before the test contained 333 and 571 mg. of phosphate, respectively. On the third day, 15 mg. of calcium ion as calcium gluconate per kilogram was administered intravenously in 1,000 cc. of saline over a four-hour period. The urinary excretion of phosphate over the next twenty-four hours was 1,233 mg. This marked increase was felt to be consistent with hypoparathyroidism. On the day after the intravenous calcium loading test, the urinary excretion of phosphate fell markedly toward the normal level.

DISCUSSION

Case 1 is a patient with idiopathic hypoparathyroidism who was first seen because of a seizure problem. These seizures, in retrospect, represented episodes of tetany. The presence of hypocalcemia was suggested by the electrocardiographic finding of an increased Q-T interval, but serum calcium determinations were not confirmatory. It was not until ten years later that the clinical diagnosis was made on the basis of the intracerebral calcifications, monilial infections of the corners of the mouth and finger nails, the long history of tetany, lenticular opacities, and failure of the secondary teeth to erupt. Confirmation of this diagnosis was then made by further laboratory studies. Case 2 is an example of subclinical hypoparathyroidism in that gross tetany and Chvostek and Trousseau signs were absent. However, on occasion, serum calcium was as low as 7.5 mg. per cent and serum phosphorus as high as 7.9 mg. per cent. The increase in phosphate excreted in the urine during the twenty-four hours following calcium infusion confirmed the diagnosis of hypoparathyroidism.

When intracranial calcification is encountered in the basal ganglia, cerebral convolutions, or dentate nucleus, the possibility of hypoparathyroidism should be considered. Hypoparathyroidism is an uncommon disease. Drake and associates[1] have set forth the following criteria now held necessary to make this diagnosis:

1. Low serum calcium concentrations
2. High serum inorganic phosphorus concentrations
3. Absence of renal insufficiency
4. Absence of roentgenologic evidence of rickets or osteomalacia
5. Absence of chronic diarrhea or steatorrhea
6. Chronic or latent tetany.

However, the diagnosis of hypoparathyroidism is at times difficult to make because serum calcium concentrations are not invariably low and serum phosphorus concentrations not always high. Rose[2] believes that it is the ionized calcium fraction of the total serum calcium that is low in hypoparathyroidism. Prasad[3] has shown that ultrafiltrable calcium is reduced in hypoparathyroidism. Since the determination of either ultrafiltrable calcium or ionized calcium is beyond the resources of hospital clinical chemistry laboratories, it may be necessary in suspected cases to repeat serum calcium and phosphorus determinations several times in order to pick out those occasions when hypocalcemia and/or hyperphosphatemia are present.

Kyle, Schaaf, and Canary[4] have shown that the clearance of phosphate is low in patients with hypoparathyroidism compared to normal subjects and feels that this is a reliable diagnostic test. Other investigators[5–8] have shown that, after an intravenous calcium load, the twenty-four-hour urinary excretion of phosphate increases markedly as compared with the base-line urinary phosphate excretion. These additional studies may be helpful in confirming the diagnosis of hypoparathyroidism.

A recent review of the literature by Bronsky and associates[9] cites 90 cases which fulfill Drake's criteria; 4 of 50 cases of idiopathic hypoparathyroidism and 5 of 40 cases of pseudohypoparathyroidism included intracranial calcification. Danowski, Lasser, and Wechsler[10] reported 93 patients with idiopathic hypoparathyroidism, 20 of whom had calcification of the basal ganglia. In addition, he reported 26 cases of basal ganglia calcification among 61 patients with pseudohypoparathyroidism and 2 cases with a similar roentgenographic appearance in 33 cases of pseudopseudohypoparathyroidism.

Sugar[11] discusses epilepsy, mental retardation, psychiatric disturbances, papilledema, cerebral calcification, and signs such as cord bladder, ataxia, tremor, hyperreflexia, and electroencephalographic abnormalities as neurologic complications of hypoparathyroidism. He points out that hypoparathyroidism per se does not cause epilepsy but that low serum calcium concentrations induce seizures in persons already predisposed to epilepsy. Cerebrospinal fluid calcium concentrations were found to be within normal limits in his series. Neurologic signs such as cord bladder, ataxia, tremor, and hyperreflexia disappeared after appropriate therapy. Electroencephalograms may be normal or abnormal. Some electroencephalographic abnormalities revert upon infusion of calcium, some revert upon prolonged oral vitamin

D therapy, and some abnormalities remain despite all therapeutic measures.

Bennet, Maffly, and Steinbach[12] state that 20% of the patients with intracranial calcification manifest symptoms of parkinsonism or athetosis. Matthews' case[13] included progressive extrapyramidal symptomatology. It is noteworthy that the severity of the symptomatology is not related to the density of the calcification. This is evidenced by a sibling of the aforementioned patient who had slightly more dense calcification but had less severe neurologic signs.

Roentgenologically, the calcifications vary in density and location. Early findings are small, irregular, discrete areas of increased density. Later, a wavy, curvilinear appearance is noted. The densities converge downward and inward and sometimes have a striated appearance. In the later stages, the shadows become larger, heavier, and homogeneous. In many cases, pneumoencephalographic studies demonstrate the shadows to be in contact with the ventricles, the calcification being in the caudate nuclei. In other cases, the calcification is more posterior and lateral and appears to be in the globus pallidus or putamen.[14] Sammet and Bucy[15] believe that the calcification is in the internal capsule rather than the basal ganglia. It is probable that the calcification is present in all the structures mentioned. Not infrequently, calcification of the dentate nuclei is also noted. The pneumoencephalogram is useful in distinguishing calcification of the basal ganglia from calcification of the choroid plexus. In the latter, the calcification appears more posteriorly and will be found to be intraventricular.

The gross pathologic findings in the few cases that have come to autopsy are described as calcareous replacement of the basal ganglia with hard masses of rocklike material. On histologic section, deposition of a homogeneous basophilic material is noted in and about the media and adventitia of the small cerebral arteries. Subsequent calcification in this basophilic material occurs. In addition, foci of concretions appear to lie free in the tissue. Some concretions demonstrate concentric layering. There is no evidence of gliosis or demyelination. Some observers have noted degeneration of the ganglion cells.[16]

SUMMARY

The causes of intracranial calcification are listed, and two new cases of intracranial calcification related to hypoparathyroidism are reported. The diagnosis of hypoparathyroidism is discussed. The clinical manifestations, roentgenographic picture, and pathologic findings are presented. In those cases of intracranial calcification where basal ganglia, convolutional, or dentate nuclear calcification is prominent, the diagnosis of hypoparathyroidism should be pursued.

REFERENCES

1. Drake, T. G., Albright, F., Bauer, W., and Castleman, R.: Chronic idiopathic hypoparathyroidism; report of 6 cases with autopsy findings in one. Ann. Int. Med. 12:1751, 1939.
2. Rose, A.: Personal communication.
3. Prasad, A. S.: Studies on ultrafilterable calcium. Arch. Int. Med. 105:560, 1960.
4. Kyle, L. H., Schaaf, M., and Canary, J. J.: Phosphate clearance in the diagnosis of parathyroid dysfunction. Am. J. Med. 24:240, 1958.
5. Howard, J. E., Hopkins, T. R., and Connor, T. D.: On certain physiologic responses to intravenous injection of calcium salts into normal, hyperparathyroid and hypoparathyroid persons. J. Clin. Endocrinol. 13:1, 1953.
6. Baylor, C. H., Van Alstine, H. E., Keutmann, E. H., and Bassett, S. H.: The fate of intravenously administered calcium. Effect on urinary calcium and phosphorus, fecal calcium and calcium-phosphorus balance. J. Clin. Invest. 29:1167, 1950.
7. Nordin, B. E. C., and Fraser, R.: The effect of intravenous calcium on phosphate excretion. Clin. Sc. 13:477, 1954.
8. Goldman, R., and Bassett, S. H.: Effect of intravenous calcium gluconate upon the excretion of calcium and phosphorus in patients with idiopathic hypoparathyroidism. J. Clin. Endocrinol. 14:278, 1954.
9. Bronsky, D., Kushner, D. S., Dubin, A., and Snapper, I.: Idiopathic hypoparathyroidism and pseudohypoparathyroidism: Case reports and review of the literature. Medicine 37:317, 1958.
10. Danowski, T. S., Lasser, E. C., and Wechsler, R. L.: Calcification of basal ganglia in post-thyroidectomy hypoparathyroidism. Metabolism 9:1064, 1960.
11. Sugar, O.: Central neurological complications of hypoparathyroidism. Arch. Neurol. & Psychiat. 70:86, 1953.
12. Bennet, J. C., Maffly, R. H., and Steinbach, H. L.: The significance of bilateral basal ganglia calcification. Radiology 72:368, 1959.
13. Matthews, W. B.: Familial calcification of the basal ganglia with response to parathormone. J. Neurol. Neurosurg. & Psychiat. 20:172, 1957.
14. Camp, J. D.: Symmetrical calcification of the cerebral basal ganglia. Radiology 49:568, 1947.
15. Sammet, J. F., and Bucy, P. C.: Symmetrical calcifications in the anterior limb of the internal capsules without demonstrable neurological or metabolic disturbances. Am. J. Roentgenol. 66:880, 1951.
16. Eaton, L. W., Camp, J. D., and Love, J. G.: Symmetric cerebral calcification, particularly of the basal ganglia, demonstrable roentgenographically. Arch. Neurol. & Psychiat. 41:921, 1939.

Spread of sodium fluorescein in normal brain tissue

A study of the mechanism of the blood-brain barrier

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THE PURPOSE of this study was to assess the concept that the lack of extracellular space in the central nervous system is responsible for the phenomenon of the blood-brain barrier.[1,2] If this concept were true, a substance normally not crossing the blood-brain barrier, but entering such specialized regions as the area postrema, would be confined to these regions and would not diffuse into surrounding brain tissue. On the other hand, if the blood-brain barrier were dependent on the properties of the walls of the cerebral blood vessels, a substance normally not crossing the barrier, but entering the area postrema, would not be confined to this region but would diffuse into surrounding brain tissue. To test these hypotheses, we administered sodium fluorescein intravenously to cats and studied the distribution of this material in the area postrema and surrounding medulla. By devising this type of experiment, we sought to avoid the criticism leveled at other investigations of this problem in which the material tested was introduced into the subarachnoid space[3–5] or placed in contact with damaged brain tissue.[6–10] In both these types of experiments, there was evidence of spread of the material into brain tissue. However, these observations were considered not entirely convincing because they were based on unphysiologic conditions.

MATERIAL AND METHODS

Under Nembutal anesthesia, 34 cats were given 20% sodium fluorescein intravenously and killed immediately or at intervals up to twenty-two hours after the administration of this dye, by the following method. The chest was rapidly opened, the ascending aorta cannulated through the left ventricle, the descending aorta clamped, the right ventricle incised, and perfusion through the cannula carried out with 200 cc. of 10% formalin under a pressure of 1.5 meters. The procedure from the opening of the chest until the end of the perfusion took ten minutes. The brain was removed immediately thereafter, this procedure taking a further ten minutes. Blocks of medulla measuring 2 mm. in thickness were immediately taken from the region of the area postrema and freeze-dried in accordance with the technic described by de Bruyn, Robertson, and Farr.[11] The block of tissue was frozen in isopentane which had been cooled in liquid air, then dehydrated in vacuo at -40° C., and embedded in paraffin in vacuo. Sections were cut at 5 μ, floated on a slide in 13% paraffin in xylol and then, with the cover slip added, sealed in paraffin.

The sections were examined with a fluorescent microscope using a high-pressure mercury arc source of ultraviolet light with a Jena B.G.-12 blue-violet transmitting filter at the light source, a Jena O.G.-1 ultraviolet absorbing filter at the eyepiece, and a bright-field condensor. The pictures were taken either on high-speed daylight Ektochrome film (ASA 160), using an exposure time of ten seconds for low power and thirty seconds for high power, or on Kodak Royal Pan film (ASA 160) with corresponding exposure times of four and fifteen minutes.

The animals were divided into 2 groups; 1 group (17 cats) received sodium fluorescein in a dose of 5 cc. per kilogram of body weight,

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This work was supported by a grant from the National Research Council of Canada.

and the second group (17 cats) received a dose of 1 cc. per kilogram of body weight. The first group of animals exhibited signs of toxicity manifested by vomiting and death after several hours, while none of the animals in the second group showed any signs of toxicity and, if not sacrificed, would awaken in a healthy state. The results in both groups were the same with the exception that in the first group the staining was more intense and prolonged.

RESULTS

In 4 cats killed within fifteen minutes of injection of sodium fluorescein, the fluorescence was very bright in the area postrema and extended into the adjacent medulla in the form of a narrow band measuring approximately 250 μ (Fig. 1A).

In 10 cats killed between thirty and ninety minutes after the injection of sodium fluorescein, fluorescence of the area postrema was somewhat less bright, but a wider zone of fluorescence was seen surrounding the area postrema; this zone gradually faded into the surrounding medulla (Fig. 1B).

In 8 cats killed between one and one-half and two and one-half hours after injection of sodium fluorescein, the zone of fluorescence extended far away from the area postrema into the surrounding medulla for a distance of 1 to 1.5 mm. (Fig. 1C).

Of 5 cats killed between two and one-half and three and one-half hours after injection of sodium fluorescein, 3 had received 5 cc. of sodium fluorescein per kilogram and still exhibited bright fluorescence of the area postrema and surrounding medulla over approximately the same area as in the previous group. However, 2 animals which received 1 cc. per kilogram showed fading fluorescence of the area postrema and only very slight fluorescence of the surrounding medulla (Fig. 1D).

Of 7 cats killed between three and one-half and twenty-two hours after injection of sodium fluorescein, 4 had received 5 cc. per kilogram and showed the same bright fluorescence of the area postrema and surrounding medulla as seen earlier. None of these animals survived longer than six hours and, if not sacrificed before this time, would invariably die. However, the 3 animals which received 1 cc. per kilogram showed no signs of toxicity and awakened from anesthesia in a healthy state; 1 of these animals was not killed until twenty-two hours had elapsed after the injection of fluorescein. None of these animals showed fluorescence of the area postrema and surrounding medulla (Fig. 1E). However, fluorescence was visible in systemic viscera as long as seven hours after this dose of fluorescein had been injected.

High-power examination of the area postrema and medulla at the height of fluorescence showed bright fluorescence of the basement membranes of capillaries and of the thick glial processes in the area postrema (Fig. 2A). In addition, there was diffuse fluorescence of the neuropil and of the nuclei and cell bodies. In particular, the nerve cells about the area postrema showed a definite fluorescence of the nucleoli and Nissl substance (Fig. 2B).

DISCUSSION

The proponents of the concept that the blood-brain barrier is due to the lack of brain extracellular space have based their views on the lack of brain intercellular space and/or the lack of brain perivascular space. However, our results indicate that sodium fluorescein can move easily in brain once allowed to cross the blood vessel wall. This movement may occur across the plasma membranes of the brain cells and/or through the narrow spaces (200 Å) in between the brain cells. Sodium fluorescein, when it does diffuse out into the medulla, is seen in the nucleoli and Nissl substance of the nerve cells. Thus, it is possible that movement may occur through the plasma membranes of the brain cells, though our results are not incompatible with the view that movement may also occur in the narrow spaces in between the brain cells. At any rate, the paucity of space in between the brain cells does not prevent movement of sodium fluorescein.

It is true that electron microscopy has shown that regions of brain devoid of a blood-brain barrier, for example, the area postrema, do have a perivascular space—the plasma membranes of the glial cells are not closely applied to the capillary basement membranes, as occurs in the gray matter of the central nervous system. However, if this close application of the plasma membranes of glial cells were the

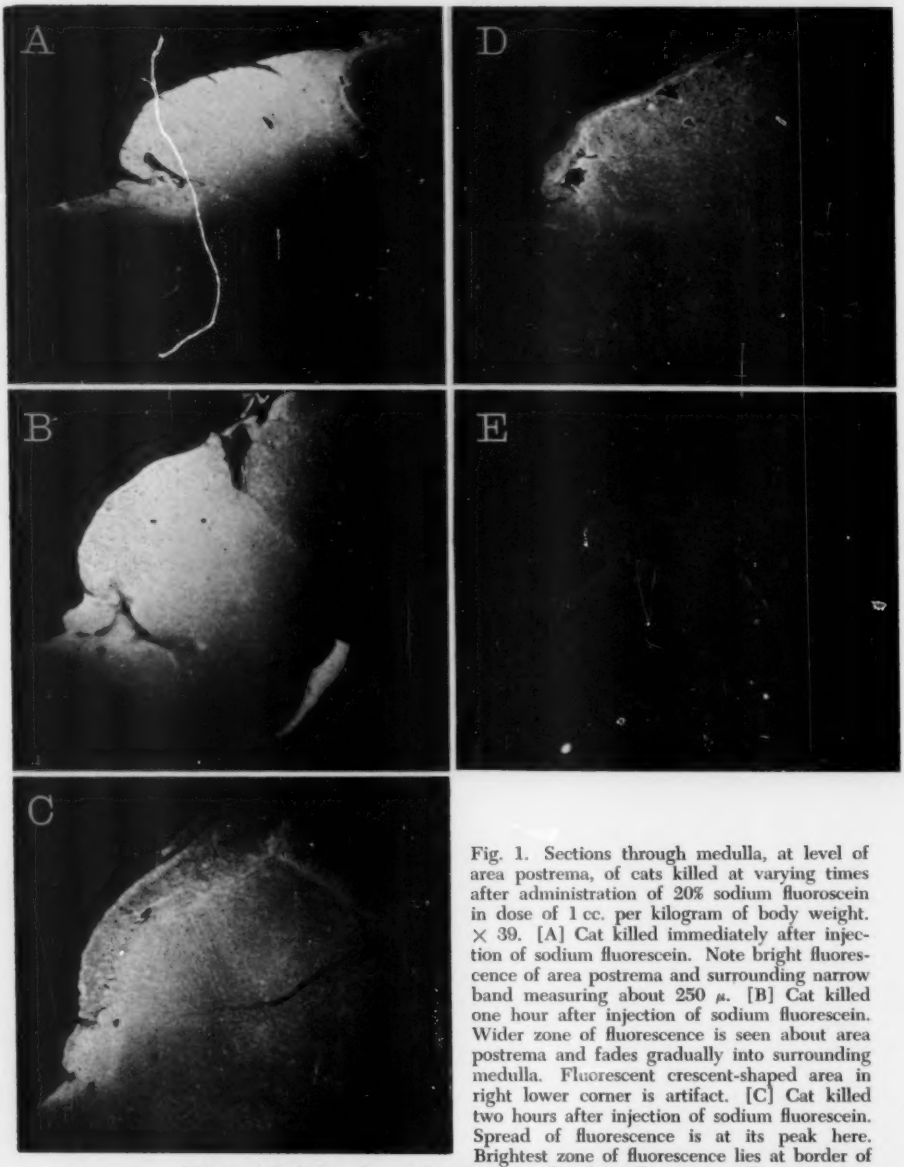

Fig. 1. Sections through medulla, at level of area postrema, of cats killed at varying times after administration of 20% sodium fluoroscein in dose of 1 cc. per kilogram of body weight. × 39. [A] Cat killed immediately after injection of sodium fluorescein. Note bright fluorescence of area postrema and surrounding narrow band measuring about 250 μ. [B] Cat killed one hour after injection of sodium fluorescein. Wider zone of fluorescence is seen about area postrema and fades gradually into surrounding medulla. Fluorescent crescent-shaped area in right lower corner is artifact. [C] Cat killed two hours after injection of sodium fluorescein. Spread of fluorescence is at its peak here. Brightest zone of fluorescence lies at border of area postrema. [D] Cat killed three hours after injection of sodium fluorescein. Fluorescence is fading and is now limited to area postrema and narrow band of medulla about it. [E] Cat killed four and one-quarter hours after injection of sodium fluorescein. Fluorescence has now completely faded.

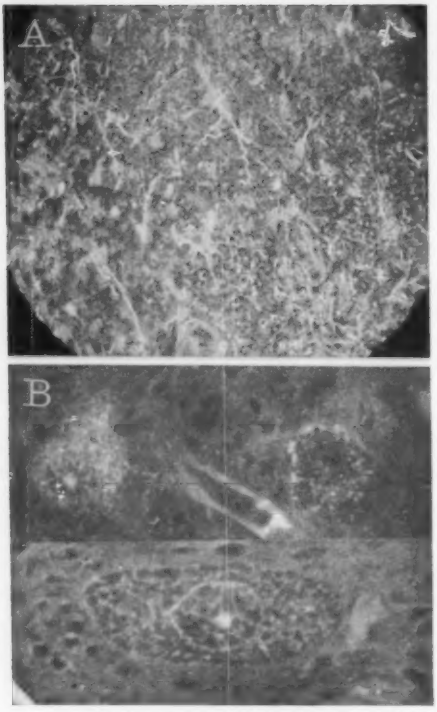

Fig. 2. [A] high-power photograph (× 500) from section reproduced in Figure 1C. Bright fluorescence of glial processes and cell bodies of astrocytes in area postrema. There is diffuse, though less intense, fluorescence of background. [B] High-power photograph (× 1,000) from section reproduced in Figure 1C. Fluorescence of nucleoli and Nissl substance of nerve cells in medulla surrounding area postrema. Fluorescence of a capillary wall is also seen in center of picture.

cause of the phenomenon of the blood-brain barrier, it would mean that the plasma membrane abutting on the capillary wall has properties different from those of the plasma membrane abutting on an adjacent brain cell. The basis of the blood-brain barrier would then not be the absence of perivascular space but the special properties of these particular cell membranes. This would bring us back to the concept that the modern counterpart of the old pia-glia membrane,[12] that is, plasma membrane ensheathing the capillaries, is the locus of the blood-brain barrier.

On the basis of the above deductions, we can safely conclude that the blood-brain barrier rests neither on the paucity of intercellular space nor on the absence of perivascular space in the brain.

Dempsey and Wislocki[13] and van Breemen and Clemente[14] observed that silver particles were present in the medulla surrounding the area postrema in rats fed silver nitrate for a prolonged period. They were unable to state whether these particles reached this region by direct migration from the area postrema or because the blood vessel walls in this region were specifically permeable to silver. Our studies confirm these observations and indicate that the route taken is direct spread from the area postrema, since fluorescence is seen to spread gradually away from the area postrema with increasing time.

It should be mentioned finally that the spread of sodium fluorescein cannot be considered a postmortem artifact. This can be ruled out because the amount of spread was found to be consistently related to the survival time, and the time between the death of the animal and the freezing of the tissue was kept constant.

SUMMARY

Sodium fluorescein was administered intravenously to healthy cats. The animals were killed at varying intervals, and sections of medulla through the area postrema were prepared using the freeze-drying technic and studied with the fluorescent microscope. The fluorescent material was seen to enter the area postrema and spread into the surrounding medulla, the extent of spread being directly related to the time which elapsed between the administration of the dye and the death of the animal. The fact that this material, which normally does not cross the blood-brain barrier, could move in tissue characterized by the presence of the barrier indicated to us that the paucity of brain extracellular space was not the basis of the blood-brain barrier but that in all probability the barrier was related to the physiologic properties of the cerebral blood vessels.

REFERENCES

1. MAYNARD, E. A., SCHULTZ, R. L., and PEASE, D. C.: Electron microscopy of the vascular bed or rat cerebral cortex. Am. J. Anat. 100:409, 1957.
2. EDSTROM, R.: An explanation of the blood-brain barrier phenomenon. Acta psychiat. et neurol. scandinav. 33:403, 1958.
3. GOLDMANN, E. E.: Vitalfarbung am Centralnervensystem. Berlin, G. Reimer, 1913.
4. BAKAY, L.: Studies on the absorption of dyes and radioactive phosphorus into the brain from the cerebrospinal fluid. Zentralbl. Neurochir. 12:15, 1952.
5. LEE, J. C., and OLSZEWSKI, J.: Penetration of radioactive bovine albumin from cerebrospinal fluid into brain tissue. Neurology 10:814, 1960.
6. DAVSON, H., and SPAZIANI, E.: Blood-brain barrier and extracellular space. J. Physiol. 149:135, 1959.
7. MACKLIN, C. A., and MACKLIN, M. T.: A study of brain repair in the rat by the use of trypan blue, with special reference to the vital staining of the macrophages. Arch. Neurol. & Psychiat. 3:353, 1920.
8. PRADOS, M., STROWGER, B., and FEINDEL, W.: Studies on cerebral edema. II. Reaction of the brain to exposure to air; physiologic changes. Arch. Neurol. & Psychiat. 54:290, 1945.
9. BAKAY, L.: Studies on blood-brain barrier with radioactive phosphorus. V. Effect of cerebral injuries and infarction on the barrier. Arch. Neurol. & Psychiat. 73:2, 1955.
10. ROZDILSKY, B., and OLSZEWSKI, J.: Permeability of cerebral blood vessels studied by radioactive iodinated bovine albumin. Neurology 7:270, 1957.
11. DE BRUYN, P. P. H., ROBERTSON, R. C., and FARR, R. S.: In vivo affinity of diaminoacridines for nuclei. Anat. Rec. 108:279, 1950.
12. GÄRTNER, W.: Die Blut-Liquorschranke. Ztschr. f. Biol. 86:115, 1927.
13. DEMPSEY, E. W., and WISLOCKI, G. B.: An electron microscopic study of the blood-brain barrier in the rat, employing silver nitrate as a vital stain. J. Biophys. & Biochem. Cytol. 1:245, 1955.
14. VAN BREEMEN, V. L., and CLEMENTE, C. D.: Silver deposition in the central nervous system and the hematoencephalic barrier studied with the electron microscope. J. Biophys. & Biochem. Cytol. 1:161, 1955.

Urinary excretion of trace metals in Huntington's chorea

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HUNTINGTON'S CHOREA is a hereditary disease characterized by the appearance in adult life of progressive chorea, loss of intelligence, and dementia. It is inherited in a single autosomal dominant fashion, and individuals suffering from the disease are heterozygous for the abnormal gene which produces it. The occurrence of carriers of this abnormal gene in the population is very small when compared to the occurrence of carriers of the abnormal gene which produces phenylketonuria. Approximately 1 out of 100 persons is heterozygous for the gene producing phenylketonuria,[1] while the frequency of heterozygotes for Huntington's chorea in Michigan has been estimated by Reed and Chandler[2] to be only 1 in 9,900 individuals. But, although the phenylketonuria gene is 100 times as common as the gene producing Huntington's chorea, the latter disease occurs 4 times as commonly due to its dominant form of inheritance. Each person who carries the abnormal gene for Huntington's chorea, along with its normal allele, can expect eventually to have the disease, whereas only homozygotes for the abnormal gene of phenylketonuria have that disease.

It is now possible to identify heterozygotes for phenylketonuria through the use of a phenylalanine tolerance test.[3–5] Discovery of the metabolic error which produces Huntington's chorea and the development of a reliable test for heterozygosity for the gene producing this disease would be of much greater practical importance. The usefulness of genetic counseling is at present limited by the fact that the onset of the symptoms of Huntington's chorea usually occurs after the end of the child-bearing period. At the least, a means of identifying heterozygotes well in advance of the onset of symptoms would make it possible for the physician to counsel carriers against having children and to relieve those relatives who are not carriers of the dread of eventually becoming demented. At the best, discovery of the metabolic error might lead to a treatment which, when used in time on known carriers, could prevent or ameliorate symptoms of the disease.

Efforts to discover a biochemical error in Huntington's chorea have so far been fruitless. Forrest[6] found no abnormal urinary excretion of amino acids or indole acids in patients suffering from the disease. Oliphant, Evans, and Forrest[7] administered tryptophan and 5-hydroxytryptophan to patients having Huntington's chorea and to normal individuals and found no difference in the urinary excretion of indoles by the 2 groups. Barbeau[8,9] has reported the presence of increased amounts of a catecholamine-like substance in the urine of 5 patients with Huntington's chorea and speculated that there might be an overaccumulation of dopamine in the basal ganglia. In a later investigation, however, Barbeau, Murphy, and Sourkes[10] found no increase in the urinary excretion of dopamine in this disease. Williams, Maury, and Kibler[11] observed no difference in the urinary excretion of homovanillic acid, a major terminal metabolite of dopamine, between patients with Huntington's chorea and normal controls. Studies in this laboratory[12] have also shown no difference in the urinary excretion of amino acids, indoles, and phenolic acids between patients with Huntington's chorea and normal adults.

A certain similarity in the involuntary movements, loss of intellect, and pathologic involvement of the basal ganglia between Wilson's disease and Huntington's chorea has led other investigators to study copper metabolism in

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This work was supported by a grant from the Ford Foundation.

the latter disease. Nielsen and Butt[13] found an elevated serum copper concentration in 2 patients with Huntington's chorea; intramuscular administration of dimercaprol (BAL) led to clinical improvement. Chhuttani, Chopra, and Singh[14] found a markedly elevated urinary excretion of copper in 1 of 2 brothers with Huntington's chorea. Forrest,[6] however, has reported normal serum and urinary copper concentrations in 4 patients with the disease.

The similarities between Huntington's chorea and Wilson's disease, together with the knowledge that accumulation in the brain of metals such as copper, lead, and mercury can produce neurologic disease in man, suggested a search for abnormalities in urinary trace metal excretion in Huntington's chorea. This paper reports the results of such a study.

MATERIAL AND METHODS

Urine specimens were collected from 7 patients with Huntington's chorea, from 6 psychotic control individuals, and from 9 normal adults. In every instance, the diagnosis of Huntington's chorea was based on the characteristic symptom complex, together with a history that 1 parent had suffered from the disease. Single urine specimens were obtained from 6 choreics who were patients in a hospital for the mentally ill and from 6 psychotic patients not suffering from Huntington's chorea who lived on the same wards and used the same food and water supply. Twenty-four-hour urine specimens were collected from 1 patient with the disease who lived at home, from his normal wife, and from 8 other normal adults. All specimens were collected in metal-free containers and stored at -20° C. until analyzed.

All glass and polyethylene equipment which came in contact with the original urine, with aliquots at any stage in the analytic procedure, or with metal-free reagents was rendered metal-free by allowing it to stand overnight in equal parts of concentrated nitric and sulfuric acid and then successively rinsing thoroughly in distilled water, followed by redistilled water. The creatinine concentration of each urine specimen was measured by a modification of the Jaffe reaction. The concentration of 14 trace metals in each urine was then determined by the following modification of the method of Perry and Perry.[15]

Wet ashing. An aliquot of urine containing 200 mg. of creatinine was measured into a 500-cc. Florence flask containing glass beads; 5 cc. of redistilled concentrated nitric acid was added, and the mixture was boiled cautiously in a wax bath. When the volume of the mixture was reduced to a few cubic centimeters, an additional 5 cc. of the acid was added and boiling continued. Then, 3 further 5-cc. additions of acid were made, so that a total of 25 cc. of redistilled concentrated nitric acid was used to complete the oxidation of the organic matter in each 200-mg. creatinine equivalent of urine. Next, 1 cc. of redistilled concentrated hydrochloric acid was added to the almost dry residue in the Florence flask to reduce excess nitric acid and to convert the nitrates to chlorides, and the heating was continued. The temperature of the wax bath was at no time permitted to exceed 160° C.

The dry residue was then dissolved in 150 cc. of redistilled water. An internal standard was added consisting of 1 cc. of an aqueous solution of indium chloride and nitrate which contained 22 μg. of indium per cubic centimeter. As a carrier for precipitation and as a matrix for ignition, 1 cc. of a 2.5% aqueous solution of purified aluminum chloride was added.

Precipitation of metals. Trace metals were quantitatively precipitated from the aqueous solution in the following manner: 10 cc. of 5% 8-hydroxyquinoline in 2 normal distilled acetic acid was added, and then the *p*H of the solution was adjusted to 1.90 ± 0.05 by the dropwise addition of approximately 8 normal purified ammonium hydroxide. After an hour, 30 cc. of purified 2 normal ammonium acetate was added, bringing the *p*H to approximately 4.8. Next, 2 cc. of 10% aqueous tannic acid and 2 cc. of 1% thionalide in glacial acetic acid were added. The *p*H was then readjusted to 5.10 ± 0.05 by the addition of as much as 40 cc. of approximately normal purified ammonium hydroxide, and the mixture was allowed to stand for twenty-four to forty-eight hours. Finally, the precipitate was collected on Whatman No. 50 filter paper and was washed several times with redistilled water.

The precipitate was dried in a vacuum desiccator over potassium hydroxide and phosphorus pentoxide and then was carefully scraped from the filter paper with a Teflon

spatula and transferred to a small metal-free polyethylene vial.

Spectrographic analysis. A 10-mg. portion of each precipitate was mixed in an agate mortar with 5 mg. of lithium carbonate and 5 mg. of powdered graphite. The mixture was loaded into a graphite cup electrode and burned to completion during about ninety seconds with a direct current arc at 13-amp. current on short circuit. The spectrum was recorded on Spectrum No. 2 film, which was developed in D-19 developer for three minutes at 21° C.

Each precipitate was burned in duplicate in this manner in order to increase accuracy. The remaining unburned portion of the precipitate was then dry ashed in a porcelain crucible in a muffle furnace at 425° C. for about two hours. A single 10 mg. portion of the ash was then mixed with lithium carbonate and graphite and was burned as described above. The percentage transmission for each metal line was measured on a densitometer, and intensity ratios were calculated with respect to indium.

In order to obtain standard working curves from which the metal concentrations in actual urines could be determined, known quantities of each of the 14 metals were carried through the chemical concentration and spectrographic analysis described above. Chemical concentration was carried out in triplicate on a minimum quantity of each of the 14 metals, as well as on multiples of 2, 4, 8, 20, and 40 times this minimum. Each resulting precipitate was assayed in duplicate spectrographically, and the intensity ratio for each metal was calculated with respect to the 3,039.4-A indium line. The remaining precipitate was then dry ashed, and a single spectrographic analysis was performed on the ash, with intensity for each metal being calculated with respect to the 3,258.6-A indium line. Standard working curves for each metal were then constructed relating intensity ratio to the indium internal standard to actual concentration of metal for the raw precipitates and for the dry ashed precipitates. In addition, blanks in which reagents only were carried through the chemical concentration procedure were analyzed in triplicate. Spectrographic analysis indicated that despite precautions to use metal-free equipment and purified reagents, there was some contamination with copper, iron, chromium, and tin. The intensity ratios achieved after addition of known multiples of these 4 metals were in good agreement, however, and since a sufficient quantity of each purified reagent was prepared initially to last throughout the investigation, it was assumed that the positive contamination remained constant for each urine studied.

With a few exceptions, 3 separate 200-mg. creatinine equivalent aliquots of each urine specimen were chemically concentrated and analyzed spectrographically. Urine concentrations of copper, iron, and molybdenum were calculated from intensity ratios to indium in the analyses of the raw precipitates, there being usually 6 values from which an average value was obtained. Urine concentrations of the remaining 11 metals were calculated from intensity ratios to indium in the analyses of the dry ashed precipitates, and there were usually 3 values from which an average value was obtained. In a few instances, obvious positive contamination with 1 or 2 metals had occurred during the spectrographic analysis or the specimen had been partially lost during burning. Such values were omitted from the calculation of average values.

RESULTS

The concentrations of the 14 metals studied are shown in Table 1 for the urines of 9 normal adults, 7 patients with Huntington's chorea, and 6 hospitalized psychotic adults. Normal subject J.E. was the wife of the choreic F.E. and, living at home with him, served as his control. The 6 psychotic patients served as environmental controls for the 6 hospitalized choreic patients. For 4 of the patients with Huntington's chorea, 2 different urine specimens, obtained three months apart, were analyzed. No significant difference was found in the urinary excretion of these 14 trace metals between patients with Huntington's chorea, their psychotic controls, and normal adults. The high concentration of iron in the urine of 2 female choreics is probably explained by contamination of the urine with a small number of red blood cells incident to catheterization, which was required to obtain urine specimens from these 2 patients. No trace metals other than calcium, magnesium, and those listed in Table 1 were found in any urine.

TABLE 1

URINARY EXCRETION OF 14 METALS IN MICROGRAMS PER 200 MG. CREATININE

Minimum measurable amount of metal				*Ag* 0.01	*Cd* 2.0	*Co* 1.0	*Cr* 0.1	*Cu* 1.5	*Fe* 0.5	*Mn* 1.0	*Mo* 1.5	*Ni* 0.8	*Pb* 0.8	*Sn* 1.0	*Ti* 3.0	*V* 0.5	*Zn* 20
Subject	*Age (yrs.)*	*Sex*	*Diagnosis*														
TP	44	M	Normal	0.07	0	•	0.6	6.8	1.9	•	7.3	2.9	2.3	14.9	0	0	505
CP	41	F	Normal	0.05	0	•	0.1	6.6	1.5	0	4.0	1.7	0.9	6.2	0	0	20
KS	41	M	Normal	0.07	0	•	•	8.2	0.8	•	6.9	8.0	1.1	8.4	0	0	130
CS	43	F	Normal	0.21	0	•	0.4	7.4	4.8	•	5.1	1.8	1.3	5.5	•	0	472
MG	35	M	Normal	0.08	0	0	0.2	6.2	1.6	0	10.5	2.0	1.3	2.9	•	0	280
EJ	41	M	Normal	0.04	0	0	•	6.5	0.6	0	5.1	1.7	1.8	5.1	0	0	483
JH	32	F	Normal	0.08	0	•	0.2	6.7	2.7	0	7.3	4.1	3.5	19.7	0	0	328
FM	68	F	Normal	0.01	0	0	0.3	10.4	2.8	0	6.1	5.1	2.0	11.4	0	0	305
JE	53	F	Normal	0.03	0	2.3	0.4	7.9	3.9	0	10.3	2.4	4.2	11.4	0	0	248
FE	56	M	Huntington's chorea	•	0	0.3	0.2	9.5	2.7	0	9.8	0.9	2.4	9.1	•	0	208
EH	43	M	Huntington's chorea	0.08	0	•	0.8	10.2	5.5	•	12.9	1.0	•	–	–	–	235
				0.02	0	0	0.1	7.2	4.6	0	12.2	1.6	1.3	5.2	0	0	525
LW	46	M	Huntington's chorea	0.01	0	•	0.3	8.0	1.6	0	6.1	2.0	•	18.0	0	0	30
				0.05	0	•	0.1	9.3	6.2	0	9.8	1.0	0.4	4.9	•	0	195
MO	54	F	Huntington's chorea	•	0	•	0.4	11.8	3.5	0	16.4	2.5	3.5	20.0	•	0	195
				0.02	0	•	0.2	12.2	44.0	0	17.9	10.9	1.8	20.9	•	–	800
MW	53	F	Huntington's chorea	•	0	•	0.2	12.9	5.0	0	14.0	7.3	1.4	23.0	0	0	145
EL	54	F	Huntington's chorea	0.03	0	0	0.4	8.4	26.0	0	13.9	2.0	1.8	10.3	–	0	560
DS	54	M	Huntington's chorea	•	0	•	0.2	11.1	12.6	0	23.0	1.6	1.1	1.8	0	0	500
				0.01	0	0	0.1	8.4	10.5	0	8.5	1.0	1.6	5.8	0	0	725
WJ	54	F	Psychotic control	0.05	0	•	0.4	6.5	4.5	•	7.8	1.3	2.0	11.2	•	0	115
DC	53	F	Psychotic control	•	0	•	0.6	8.7	2.8	•	62.0	2.5	1.0	5.2	0	0	38
RR	23	M	Psychotic control	0.04	0	0	0.2	7.4	2.2	0	17.9	1.8	1.5	11.6	•	0	1,030
TH	45	M	Psychotic control	0	0	0	0	8.3	9.4	0	4.4	0	0	3.7	0	0	•
CP	53	M	Psychotic control	•	0	4.1	0.5	19.3	6.5	•	17.5	3.4	1.3	–	0	0	250
JB	52	M	Psychotic control	•	0	•	0.1	8.8	3.1	0	8.4	2.3	0.8	15.7	0	0	618

•Metal present but amount insufficient for quantitation

TABLE 2

URINARY EXCRETION OF 14 TRACE METALS IN MICROGRAMS PER TWENTY-FOUR HOURS

Subject	*Age (yrs.)*	*Sex*	*Diagnosis*	*Ag*	*Cd*	*Co*	*Cr*	*Cu*	*Fe*	*Mn*	*Mo*	*Ni*	*Pb*	*Sn*	*Ti*	*V*	*Zn*
TP	44	M	Normal	0.68	0	•	5.8	66	18	•	71	28	22	145	0	0	4,910
CP	41	F	Normal	0.32	0	•	0.6	42	10	0	26	11	5	40	0	0	128
KS	41	M	Normal	0.72	0	•	•	84	8	•	71	82	11	86	0	0	1,332
CS	43	F	Normal	1.13	0	•	2.2	40	26	•	28	10	7	30	•	0	2,550
MG	35	M	Normal	0.65	0	0	1.6	50	13	0	86	16	11	24	•	0	2,280
EJ	41	M	Normal	0.57	0	0	•	92	9	0	72	24	26	72	0	0	6,860
JH	32	F	Normal	0.43	0	•	1.1	36	15	0	39	22	19	106	0	0	1,775
FM	68	F	Normal	0.04	0	0	0	38	10	0	23	19	7	42	0	0	1,142
JE	53	F	Normal	0.11	0	8.2	1.4	28	14	0	37	9	15	41	0	0	888
FE	56	M	Huntington's chorea	•	0	2.6	1.7	82	23	0	85	8	21	79	•	0	1,805

•Metal present but amount insufficient for quantitation

Table 2 presents the twenty-four-hour urinary excretion of trace metals by 9 normal adults and by 1 patient with Huntington's chorea. It was impossible to obtain accurate twenty-four-hour urine collections from the more seriously deteriorated hospitalized choreics. It can be seen that the twenty-four-hour urinary excretion of 14 trace metals in 1 choreic does not differ significantly from that found in normal individuals.

DISCUSSION

The sensitivity of the analytic method used in this study was insufficient for the analysis of cadmium, manganese, titanium, and vanadium. Zinc values varied considerably among replicate determinations, and the absolute concentrations of urinary zinc reported here are considered less reliable than those for the other metals found in urine in measurable amount. The concentrations of urinary tin, nickel, and molybdenum agree well with those reported for normal individuals by Perry and Perry,[15] while those of lead and silver are lower and those of zinc and chromium are higher. The higher values of urinary chromium in the present study may possibly be accounted for, since only 2% as much concentrated hydrochloric acid was used in the digestion of urines as was used by the authors cited, and loss of volatile chromyl chloride may therefore have been avoided. The twenty-four-hour urinary copper values of the normal subjects and 1 choreic in this study lie within the normal range of less than 100 μg. per day and well below the twenty-four-hour urinary copper excretions reported for patients with Wilson's disease.[16] Measurable amounts of cobalt were found in 3 urines in this study, and the amount excreted approximated that reported for normal adults by Harp and Scoular.[17] Thus, it seems preferable to use as an internal standard a rare metal not apt to be found in urine, rather than cobalt, which was added as an internal standard by the investigators.[15]

In any case, regardless of the absolute accuracy of the metal concentrations in urines, no relative difference was found between normal individuals, patients with Huntington's chorea, and other hospitalized psychotics in the urinary excretion of silver, chromium, copper, iron, molybdenum, nickel, lead, tin, and zinc. The method used was not sufficiently sensitive to quantitate cadmium, colbalt, manganese, titanium, and vanadium in all urines, but again there was no evidence of any marked difference in the excretion of these metals between normal adults and choreics. The possibility still exists that the symptoms and neuropathologic changes of Huntington's chorea may be related to an increased deposition of a toxic metal in the central nervous system or to a decreased concentration of a physiologically essential trace metal. It would be desirable to measure tissue concentration of trace metals in such organs as brain, liver, and kidney at autopsy from persons dying of Huntington's chorea.

SUMMARY

The urinary excretion of 14 trace metals has been studied by a spectrochemical technic in normal adults, in persons suffering from Huntington's chorea, and in other psychotics. No significant difference in the excretion of trace metals between the 3 groups was found. The possibility, suggested by other investigators, that Huntington's chorea involves an abnormality in copper metabolism was not confirmed.

The author is indebted to Dorothy Walker for technical assistance; to Hal W. Johnson of the Pacific Spectrochemical Laboratory, Los Angeles, for performing the spectrographic analyses; and to Dr. George Y. Abe, Acting Superintendent, Metropolitan State Hospital, Norwalk, for making available the hospitalized patients used in this study.

REFERENCES

1. Penrose, L. S.: The Biology of Mental Defect. 2d ed., London, Sidgwick and Jackson, Ltd., 1954, p. 147.
2. Reed, T. E., and Chandler, J. H.: Huntington's chorea in Michigan: 1. Demography and genetics. Am. J. Human Genet. 10:201, 1958.
3. Hsia, D. Y. Y., Driscoll, K. W., Troll, W., and Knox, W. E.: Detection by phenylalanine tolerance tests of heterozygous carriers of phenylketonuria. Nature 178:1239, 1956.
4. Jervis, G. A.: Detection of heterozygotes for phenylketonuria. Clin. chim. acta 5:471, 1960.
5. Lippman, R. W., Shaw, K. N. F., Perry, T. L., Gutenstein, M., Redlich, D., Moore, P., and Walker, D.: In preparation.
6. Forrest, A. D.: Some observations on Huntington's chorea. J. Ment. Sc. 103:507, 1957.
7. Oliphant, J., Evans, J. I., and Forrest, A. D.: Huntington's chorea—some biochemical and therapeutic aspects. J. Ment. Sc. 106:718, 1960.
8. Barbeau, A.: Preliminary observations on abnormal catecholamine metabolism in basal ganglia diseases. Neurology 10:446, 1960.
9. Barbeau, A.: Dopamine and basal ganglia diseases. Arch. Neurol. 4:97, 1961.
10. Barbeau, A., Murphy, G. F., and Sourkes, T. L.: Excretion of dopamine in diseases of basal ganglia. Science 133:1706, 1961.
11. Williams, C. M., Maury, S., and Kibler, R. F.: Normal excretion of homovanillic acid in the urine of patients with Huntington's chorea. J. Neurochem. 6: 254, 1961.
12. Perry, T. L., and Shaw, K. N. F.: Unpublished observations.
13. Nielsen, J. M., and Butt, E. M.: Treatment of Huntington's chorea with BAL. Bull. Los Angeles Neurol. Soc. 20:38, 1955.
14. Chhuttani, P. N., Chopra, H. L., and Singh, S.: Huntington's chorea; a biochemical study. J. Indian M. A. 32:401, 1959.
15. Perry, H. M., Jr., and Perry, E. F.: Normal concentrations of some trace metals in human urine: changes produced by ethylenediaminetetraacetate. J. Clin. Invest. 38:1452, 1959.
16. German, J. L. III, and Bearn, A. G.: Effect of estrogens on copper metabolism in Wilson's disease. J. Clin. Invest. 40:445, 1961.
17. Harp, M. J., and Scoular, F. I.: Cobalt metabolism of young college women on self-selected diets. J. Nutrition 47:67, 1952.

Increased intracranial pressure with bulging fontanel

A symptom of vitamin A deficiency in infants

Murray H. Bass, M.D., and Gilbert R. Fisch, M.D.

INCREASED CEREBROSPINAL FLUID PRESSURE is not generally recognized as one of the signs of vitamin A deficiency but is now well documented. In young infants, it is easily diagnosed by marked bulging of the fontanel. Veterinarians have long been familiar with the condition in young animals kept on a diet free of vitamin A.[1] It was first described in human infants by Blackfan and Wolbach,[2] who reported the case of a 6½-month-old infant admitted to the hospital because of drowsiness of four days' duration. The neck was retracted, and there was some separation of the sutures of the skull. The spinal fluid was normal, and the child recovered when vitamin A was given, although he remained blind as the result of the accompanying keratomalacia. In 1952, Cornfeld and Cooke[3] described a fascinating case of an allergic infant of 5½ months on a milk-free diet, among whose presenting symptoms were lack of interest in her surroundings, seemingly mental and physical retardation, unilateral facial paralysis, enlargement of the breasts, and xerosis of the cornea. During observation, bulging of the fontanel with normal cerebrospinal fluid appeared. Vitamin A deficiency was proved by low vitamin blood level. The vitamin was given parenterally in large doses, and the infant recovered, though it took several months for the fontanel to return to normal.

In 1955, Bass and Caplan[4] described 2 cases of bulging fontanel, 1 in an allergic infant on a vitamin A–free diet and the other in an infant suffering from congenital obstruction of the bile ducts, resulting in failure to absorb vitamin A. The first of these 2 babies showed particularly marked involvement of the nervous system with fever up to 104° F., so that among the suggested diagnoses were subdural hematoma, multiple cerebral septic emboli, and thrombosis of the sagittal sinus. All these signs and symptoms disappeared when large doses of vitamin A were given, and recovery was complete.

In 1958, Wolf[5] recognized and reported a case with severe keratomalacia, facial paralysis, tense fontanel, and radiographic evidence of separation of the suture lines of the skull. Vitamin A blood level was zero. The infant recovered when vitamin A was added to the diet.

Vitamin A deficiency in the human infant is not frequently observed in this country where the average diet consists of milk, which contains enough of this vitamin to render supplementation unnecessary. However, in infants allergic to milk, milk-free substitutes may not contain the vitamin, and symptoms of avitaminosis may result. Among these symptoms are the following:

- Retardation of mental and physical growth
- Anemia with or without splenomegaly
- Tendency to infection (skin and respiratory tract)
- Epithelial metaplasia:
  - In the eye: xerophthalmia and keratomalacia
  - In the urinary tract: hematuria
  - In the vagina: cornified epithelium
  - In the digestive and respiratory tracts: diarrhea, frequent infections
- Endocrine disturbance: gynecomastia
- Increased cerebrospinal pressure with bulging fontanel
- Cranial nerve injury: facial paralysis.

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This bizarre clinical syndrome is easily recognized, especially if xerophthalmia or gynecomastia is present. Among the signs and symptoms referable to the nervous system are irritability with increased reflexes, followed in some cases by mental dullness almost to the state of coma, mild nuchal rigidity, bulging fontanel, and facial paralysis. Ocular fundi are difficult to visualize, since corneal dullness is usually present. In calves, however, choked disk has been described.[1]

Little is known as to the specific action of vitamin A in spite of much experimental work on animals.[6] Dehority and his colleagues[7] preface a recent paper with this statement: "Since the initial studies of L. A. Moore and J. F. Sykes, it has become increasingly evident that the first measurable change which occurs in experimentally produced vitamin A deficiency in the calf, chick, rabbit and pig is an increase in the cerebrospinal pressure." These investigators made a very carefully controlled study of the biochemical constituents of the serum and the cerebrospinal fluid of vitamin A–deficient calves. In summarizing their work, they say, "These results do not directly explain the increased cerebrospinal fluid pressure or change in aqueous humor composition occurring in vitamin A deficiency. However, the data pertaining to cerebrospinal fluid suggest either an overproduction or underabsorption of fluid (without change in the concentration of the constituents in serum or cerebrospinal fluid), resulting in greater volume within the restricted subarachnoid space and ventricles of the central nervous system."

Several other noninflammatory conditions in benign hydrocephalus in infants must be considered in the differential diagnosis. The 2 most important are [1] an unusual reaction to tetracycline drugs and [2] intake of excessive amounts of vitamin A (vitamin A poisoning). The former was first mentioned by Gellis[8] in 1956. Recently, 2 cases of bulging fontanel due to ingestion of tetracycline were reported in detail by Fields,[9] who says, "The relationship between tetracycline therapy and increased intracranial pressure seems to be more than coincidental." After medication was discontinued, the bulging fontanel returned to normal after a few hours.

We have recently seen this condition in an 11-month-old infant who for two days had received tetracycline (80 mg. per kilogram per day). On the second day, the child was admitted to the hospital and meningitis was suspected. However, the urine, a complete blood count, and the spinal fluid were all normal. Drug idiosyncrasy was suspected, and all drugs were stopped. After twenty-four hours, the fontanel had returned to normal.

Curiously enough, the intake of *excessive* amounts of vitamin A may also result in bulging of the fontanel in infants and give rise to symptoms referable to the nervous system in older individuals.[10,11] The cases of several infants were reported by Marie and See[12] in 1954; the patients were brought to the physician on account of marked bulging of the fontanel, restlessness, insomnia, or drowsiness. The infants had received huge doses of vitamins A and D. The authors were able to reproduce the symptoms in 3 infants and in puppies by giving vitamin A alone. A number of similar cases have since been reported by others.

Bulging fontanel with normal spinal fluid has recently been described as occurring during the course of roseola infantum.[13]

CASE REPORT

Case 1. K. B., a female infant, was born at term by spontaneous delivery. Birth weight was 7 lb. Because of a history of milk allergy in siblings, the infant was immediately put on a milk-free diet (Mull-Soy) without vitamin supplement. At the age of 3½ months, the infant was brought to the physician's office on account of marked enlargement of the breasts. No diagnosis was made, and the mother was told to return in two weeks. However, at that time, the physician was asked to see the baby at home since she had become extremely irritable and had a temperature of 100.5° F. The child appeared pale and extremely restless but did not look acutely ill. The breasts were still enlarged. There was marked bulging of the fontanel. The child had received no drugs. Meningitis was suspected, and the child was hospitalized. Lumbar puncture revealed bloody fluid under high pressure. A bloody tap was suspected. Culture of the fluid showed no growth. Complete blood count and blood culture were normal. Blood chemistry was with-

in normal limits. Vitamin A deficiency was suspected, and blood was drawn for vitamin A content, but the specimen was unfortunately lost in the laboratory. Urine could not be examined because the urethral opening could not be located on account of excessive cornified epithelium. Penicillin was administered without improvement. Vitamin A was then given daily. In one day, the child's disposition had improved and the fontanel was softer. The next day the child was eating, the fontanel was flatter, and the temperature was normal. During the next few weeks, the gynecomastia gradually disappeared and the child made a perfect recovery.

Case 2. E. R., a Puerto Rican male infant, was under treatment for severe eczema which had appeared at the age of 1 month. Pregnancy and labor had been normal. He had been on a milk formula without any vitamin supplement and had recently lost weight and refused food. At 2 months of age, conjunctivitis was noted. As the eczema had not yielded to local treatment, milk allergy was suspected, and, at the age of 3 months, a soybean preparation (Mull-Soy) was prescribed. The infant did poorly and lost weight, and the conjunctivitis became more severe, leading to the diagnosis of keratoconjunctivitis with denuding of the cornea. The infant became more and more lethargic, and signs of mild rickets appeared which were corroborated by blood chemistry and bone roentgenograms. At this time, the anterior fontanel, which had been soft and flat, showed marked bulging. A lumbar puncture revealed normal clear fluid under high pressure. Urinalysis and blood counts were normal. Blood drawn for vitamin A level showed 28 μg. per cent (normal, 45 to 150). A loading test for vitamin A was given and showed a four-hour blood level of 447 and a six-hour level of 172 μg. This rapid uptake is characteristic of hypovitaminosis. Serum carotene was 12 μg. per cent, (normal, 60 to 80). A deficiency of vitamins A and D having been established, the patient was given combined vitamins (Poly-Vi-Sol, 1.2 cc. three times a day).

Within three days, the conjunctivae were clear and the cornea glistening. The severe lethargy disappeared, and the child became playful and active. There was marked improvement in the skin rash. The fontanel, however, remained tense and bulging. Two weeks after vitamin therapy was started, roentgenograms showed healing rickets and the blood calcium, phosphorus, and alkaline phosphatase had returned to normal levels. The course thereafter was marked by progressive gain and normal behavior. The fontanel for a time remained full and then slowly became softer and flatter, so that after thirty days it had returned to normal and the infant appeared well.

DISCUSSION

Case 1. This infant had been on a vitamin A–free diet for several months. The case is of interest because the enlargement of the breasts antedated the symptoms referable to the nervous system. The triad of gynecomastia, epithelial hyperplasia of the vaginal mucosa, and increased cerebrospinal fluid pressure, together with the rapid response when vitamin A was given, leaves no question as to the diagnosis.

The presence of gynecomastia is interesting and may well be due to some obscure relationship between vitamin A and some female sex hormone. In a report on the beneficial effect of progesterone on pregnancy in the vitamin A–deficient rabbit, Hays and Kendall[14] say, "It is possible that vitamin A and progesterone are involved in some physiological process essential to the maintenance of pregnancy and that injected progesterone may be substituted at least in part for vitamin A."

Case 2. The prompt improvement of the severe ocular lesion and the rapid change in the infant's reaction to its environment when vitamin A was given are characteristic. The persistence of the bulging fontanel for a month was also present in a case of vitamin A deficiency previously described.[3] This differs from the prompt disappearance of evidence of the increased cerebrospinal pressure due to drugs.

SUMMARY

Vitamin A deficiency in infants may result in a bizarre clinical picture including symptoms referable to the nervous system due to increased intracranial pressure. This condition should be more widely recognized, since, if untreated, it may lead to a very serious and

possibly fatal outcome. However, when diagnosed, the condition may be easily and rapidly cured by administration of vitamin A. The symptoms are so varied and involve so many organs that the clinical picture should be familiar not only to the pediatrician but to the neurologist, allergist, oculist, and urologist as well. Two cases are reported.

The authors are indebted to Dr. Christine Pegg of Port Washington, Long Island, New York, for permission to report Case 1.

REFERENCES

1. Moore, L. A., and Sykes, J. F.: Cerebrospinal fluid pressure and vitamin A deficiency. Am. J. Physiol. 130:684, 1940.
2. Blackfan, J. D., and Wolbach, S. B.: Vitamin A deficiency in infants: Clinical and pathological study. J. Pediat. 3:679, 1933.
3. Cornfeld, D., and Cooke, R. E.: Vitamin A deficiency: Case report; unusual manifestations in a 5½ month old baby. Pediatrics 10:33, 1952.
4. Bass, M. H., and Caplan, J.: Vitamin A deficiency in infancy. J. Pediat. 47:690, 1955.
5. Wolf, I. J.: Vitamin A deficiency in an infant. J.A.M.A. 166:185, 1958.
6. Millen, J. W., Woolam, D. H. M., and Lamming, G. E.: Hydrocephalus associated with deficiency of vitamin A. Lancet 2:1234, 1953; Congenital hydrocephalus due to experimental hypovitaminosis A. Lancet 2:679, 1954.
7. Dehority, B. A., and associates: Some biochemical constituents in serum; cerebrospinal fluid and aqueous humor of vitamin A deficient Holstein calves. J. Dairy Science 43:630, 1960.
8. Gellis, S. S.: Note. In Year Book of Pediatrics. Chicago, Year Book Publishers, Inc., 1956-57, p. 40.
9. Fields, J. P.: Bulging fontanel: a complication of tetracycline therapy in infants. J. Pediat. 58:74, 1961.
10. Morrice, G., Jr., Havener, W. H., and Kapetansky, F.: Vitamin A intoxication as a cause of pseudotumor cerebri. J.A.M.A. 173:1802, 1960.
11. Bass, M. H.: The relation of vitamin A to cerebrospinal fluid pressure: A review. J. Mount Sinai Hosp. 24:713, 1957.
12. Marie, J., and See, G.: Acute hypervitaminosis A of the infant. Am. J. Dis. Child. 87:731, 1954.
13. Oski, F. A.: Roseola infantum: Another cause of bulging fontanel. Am. J. Dis. Child. 101:376, 1961.
14. Hays, R. L., and Kendall, K. A.: The beneficial effect of progesterone on pregnancy in the vitamin A-deficient rabbit. J. Nutrition 59:337, 1956.

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OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF NEUROLOGY

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*Ayd, Frank J., Jr.: Drug-induced Extrapyramidal Reactions: Their Clinical Manifestations and Treatment with Akineton. Psychosomatics 1:143 (May-June) 1960.

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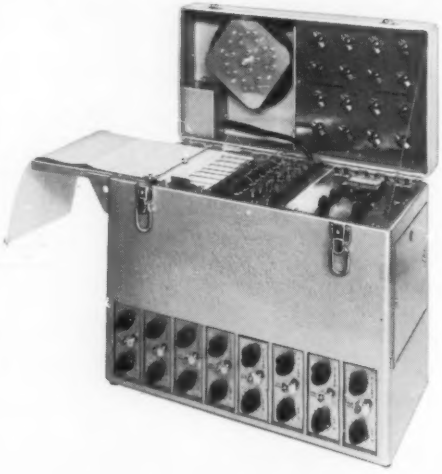

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NEWSLETTER

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DECEMBER 1961

Association for Research in Nervous and Mental Disease The annual meeting of the Association for Research in Nervous and Mental Disease will be held at the Hotel Roosevelt, New York City, on Friday and Saturday, December 8 and 9, 1961. The subject of the meeting will be "Cerebrovascular Disease," and the officers are as follows: President, Dr. Clark H. Millikan; Vice-President, Dr. Irving S. Wright; Vice-President, Dr. Seymour S. Kety; Secretary-Treasurer, Dr. Rollo J. Masselink; Assistant Secretary-Treasurer, Dr. Arnold J. Friedhoff.

American Epilepsy Society The annual meeting of the American Epilepsy Society will be held in New York City on December 7, 1961, in the Sert Room of the Waldorf-Astoria Hotel. In the morning, a symposium has been planned on the subject, "Epilepsy in Infancy and Childhood," and the afternoon will be devoted to scientific contributions on various subjects related to epilepsy. The officers of the society are as follows: President, Dr. William F. Caveness; President-elect, Dr. Theodore B. Rasmussen; Secretary, Dr. Richard P. Schmidt; Treasurer, Dr. James W. Crawley. Dr. J. Preston Robb is the Chairman of the Program Committee.

American Board of Psychiatry and Neurology The following were certified in neurology by the American Board of Psychiatry and Neurology, Inc., at the time of the examinations in Chicago on October 7, 9, and 10, 1961: Dr. Wilmer M. Anderson, Philadelphia; Dr. Howard S. Barrows, Arcadia, Calif.; Dr. Jerome M. Block, New York City; Dr. Richard F. Daly, Memphis; Dr. Robert W. Egan, Brookline, Mass.; Dr. David Green, New York City; Dr. Rose Mary Jaros, Kensfield, Calif.; Dr. Jonas V. Mileris, Aurora, Ill.; Dr. John S. Sewell, Orlando, Fla.; Dr. August G. Swanson, Seattle; Dr. Richard C. Turrell, Louisville; Dr. Stuart Weiss, St. Louis.... At a business meeting of the Board held in Chicago on October 8, 1961, the following regulation was passed: After June 30, 1962, all applicants for eligibility for examination in psychiatry and/or neurology by the American Board of Psychiatry and Neurology, Inc., must present three years of full-time approved

residency training credit in order to fulfill the training requirements. After this date, the regulation permitting ante-1934 graduates to substitute ten years of full-time experience in lieu of formal residency training credit will be terminated.... The following examinations will be held by the American Board of Psychiatry and Neurology, Inc.: New York City, December 9, 11, and 12, 1961; San Francisco, March 31 and April 2 and 3, 1962; and Detroit, October 13, 15, and 16, 1962.

Postgraduate Courses and Training Programs A course in pediatric neurology will be held at the Center for Continuation Study, University of Minnesota, February 12 through 14, 1962. Further information may be obtained from the Director, Department of Continuation Medical Education, 1342 Mayo Memorial, Minneapolis 14, Minn.... New York University Medical Center is offering a three-month training fellowship in neuroanatomy and neurophysiology, with a stipend of about $1,000, beginning March 1, 1962. Candidates holding the M.D. or Ph.D. degree and interested in teaching or research in these subjects are eligible. Applications should be in by January 1, 1962. For information apply to Dr Louis Hausman, Department of Anatomy, New York University School of Medicine, New York University Medical Center, 550 First Avenue, New York City 16.... The Mayo Foundation and Clinic have established a training program leading to a career in pediatric neurology. This is directed by Dr. J. Gordon Millichap and planned according to the outline of training suggested by the American Board of Pediatrics and the American Board of Psychiatry and Neurology. Assignments in adult neurology and in the basic sciences related to developmental neurology are included in the training program. Trainees supported by the National Institutes of Health are currently participating in this program. Inquiries may be sent to Dr. Victor Johnson, Director of the Mayo Foundation for Medical Education and Research, Rochester, Minn.... A two-day postgraduate course in clinical neurology will be held at the University of Michigan Medical Center on March 20 and 21, 1962. Sponsored by the Department of Postgraduate Medicine of the University of Michigan, this course is held under the auspices of the Department of Neurology.

Barrow Neurological Institute The Barrow Neurological Institute of St. Joseph's Hospital, Phoenix, will be open for patients, teaching, and research on July 1, 1962. The following have been appointed to the staff: The Director of the Institute (appointed in 1958 by St. Joseph's Hospital) and Chairman of the Division of Neurological Surgery is Dr. John R. Green. Dr. Green received his M.D. from Northwestern University Medical School and his training in neurologic surgery

and neurologic sciences in Chicago at St. Luke's Hospital and the University of Illinois Research and Educational Hospitals, Illinois Neuropsychiatric Institute. Dr. David D. Daly, a graduate of the University of Minnesota, where he obtained his M.D. degree and a Ph.D. in neurology, started his appointment as Chairman of the Division of Neurology and Electroencephalography on September 1, 1961. He was a consultant in neurology at the Mayo Clinic and Foundation from 1951 to 1961.... Dr. Eduardo Eidelberg, formerly Associate Research Professor of Anatomy at University of California at Los Angeles School of Medicine and presently a U. S. Public Health Service fellow at the Karolinska Institute in Stockholm, will start his appointment as Chairman of the Division of Experimental Neurology and Chief of the Neuro-Physiology Laboratory on February 1, 1962. Dr. James W. Kernohan, presently Senior Consultant in Pathology at Mayo Clinic and Foundation, will begin his appointment as Chairman of the Division of Neuro-Pathology on March 1, 1962. Dr. Helen J. Ramsey, a fellow in neuroanatomic sciences at NINDB under Dr. W. F. Windle from 1955 to 1959 and a fellow in electron microscopy under Dr. Daniel C. Pease at the University of California at Los Angeles School of Medicine since 1959, will serve as Chief of the Electron Microscopy Laboratory beginning July 1, 1962. Dr. Arthur S. Schwartz, formerly a fellow under Dr. Donald Lindsley, Professor of Psychology and Physiology at University of California at Los Angeles School of Medicine and presently working in physiologic psychology in the Department of Neuro-Pharmacology at Saint Elizabeth's Hospital, Washington, D. C., will start as Chief of the Behavior Laboratory on July 1, 1962.

Miscellaneous An International Symposium on Neurochemistry will be held at Göteborg, Sweden, June 18 through 21, 1962. Sponsored by the Commission of Neurochemistry of the World Federation of Neurology, the symposium will be entitled "Enzymic Activity in the Central Nervous System." Further information can be obtained from either of the secretaries, Dr. A. Lowenthal, Institut Bunge, 59, rue Philippe Williot, Berchem-Anvers, Belgium, or Dr. G. B. Ansell, Department of Experimental Psychiatry, Medical School, Birmingham, 15, England.... An International Society for Research in Stereoencephalotomy was founded at the time of the International Symposium on Stereoencephalotomy in Philadelphia, October 11 and 12, 1961. The following officers were elected: President, Dr. E. A. Spiegel, Philadelphia; Vice-President, Dr. T. Riechert, Freiburg, Germany; Secretary-Treasurer, Dr. H. T. Wycis, Philadelphia. The transactions of the Society will be published in CONFINIA NEUROLOGICA (Publisher: S. Karger, Basel, Switzerland). Further information may be obtained from Dr. H. T. Wycis, 3401 N. Broad Street, Philadelphia 40.... Delegates in attendance at the Seventh International Neurological Congress in

Rome, September 10 through 15, selected Vienna as the meeting place for the Eighth Congress in 1965. The Fifth International Congress of Neuropathology is to be held in Zurich in 1965.... At the meeting of the Executive Committee of the World Federation of Neurology in Rome on September 16, Dr. Ludo van Bogaert was reelected President. Drs. H. Houston Merritt and Raymond Garcin were elected to the position of Vice-President, and Dr. Pearce Bailey was reelected Secretary-Treasurer General.

Personals Dr. Walter J. Friedlander, formerly Chief of the Veterans Epilepsy Center at the Boston Veterans Administration Hospital, has been appointed Associate Professor of Neurology at the Albany College of Medicine.... Dr. Robert D. Currier, formerly Associate Professor of Neurology at the University of Michigan Medical School, has been appointed Head of the Section of Neurology in the Department of Medicine in the University of Mississippi Medical School, Jackson.... Dr. Max K. Newman of Detroit is now President-elect of the American Academy of Physical Medicine and Rehabilitation.... At the Boston University School of Medicine, Dr. Paul B. Jossmann, Chief Neurologist at the Boston Veterans Administration Outpatient Clinic, has been named Honorary Professor of Neurology.... Dr. Frederick P. Currier, a member of the American Academy of Neurology since 1948 and for many years in the practice of neurology in Grand Rapids, Mich., died on July 5, after a long illness.... Dr. Ladislav P. Hinterbucher has been appointed Director of Neurology at the Jewish Chronic Disease Hospital in Brooklyn. ... Dr. Charles E. Wells, formerly Assistant Professor of Medicine (Neurology) at Cornell University Medical School, was appointed Associate Professor of Medicine (Neurology) at Vanderbilt University School of Medicine on July 1.

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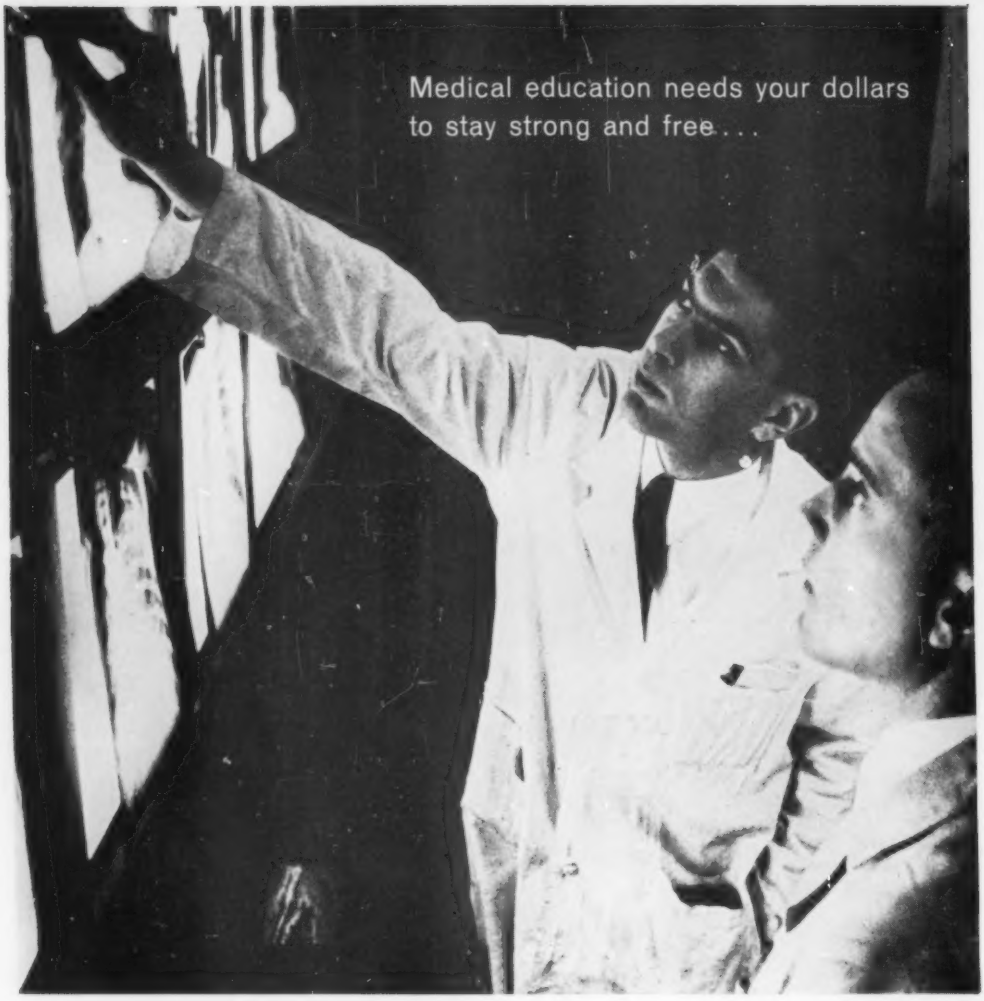
Bibliography: 1. Javid, M.; Settlage, P., and Monfore, T.: Surgical Forum *7*:528, 1957. 2. Javid, M., and Settlage, P.: Tr. Am. Neurol. A. 1957, *82*:151. 3. Javid, M.: Surg. Clin. North Am. *38*:907 (Aug.) 1958. 4. Taheri, Z. E.: J. Internat. Coll. Surgeons *32*:389 (Oct.) 1959. 5. Stubbs, J., and Pennybacker, J.: Lancet *1*:1094, 1960. 6. Katz, R. A.: New England J. Med. *262*:870 (April 28) 1960.



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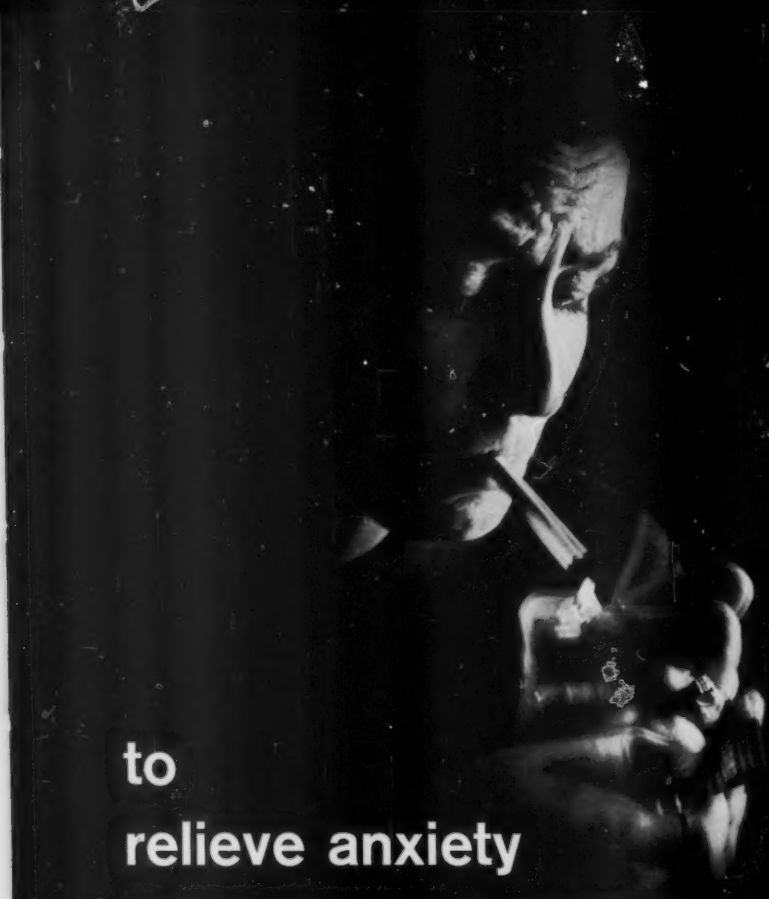

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Benztropine Methanesulfonate

without lowering phenothiazine dosage

"When rigidity and tremors are in the foreground, and especially in combination with sialorrhea...[COGENTIN] gave prompt relief in 86%..."[1] of patients with tranquilizer-induced parkinsonism. Important: With COGENTIN, parkinsonism can often be reversed without reducing phenothiazine dosage.[2] A most powerful antispasmodic,[3] its long cumulative action is unusually well tolerated.[4]

Before prescribing or administering COGENTIN, the physician should consult the detailed information on use accompanying the package or available on request.

Supplied: Tablets COGENTIN (quarterscored), 2 mg., bottles of 100 and 1000. New dose form: Injection COGENTIN, 1 mg. per cc., ampuls of 2 cc., boxes of 6.

References: 1. Kruse, W.: Dis. Nerv. System 21:79, 1960. 2. Ayd, F. J., Jr.: Clin. Med. 6:387, 1959. 3. Brock, S. (Moderator): Bull. New York Acad. Med. 32:202, 1956. 4. Dashay, L. J., and Boshes, L.: Postgrad. Med. 27:602, 1960.

COGENTIN is a trademark of Merck & Co., Inc.

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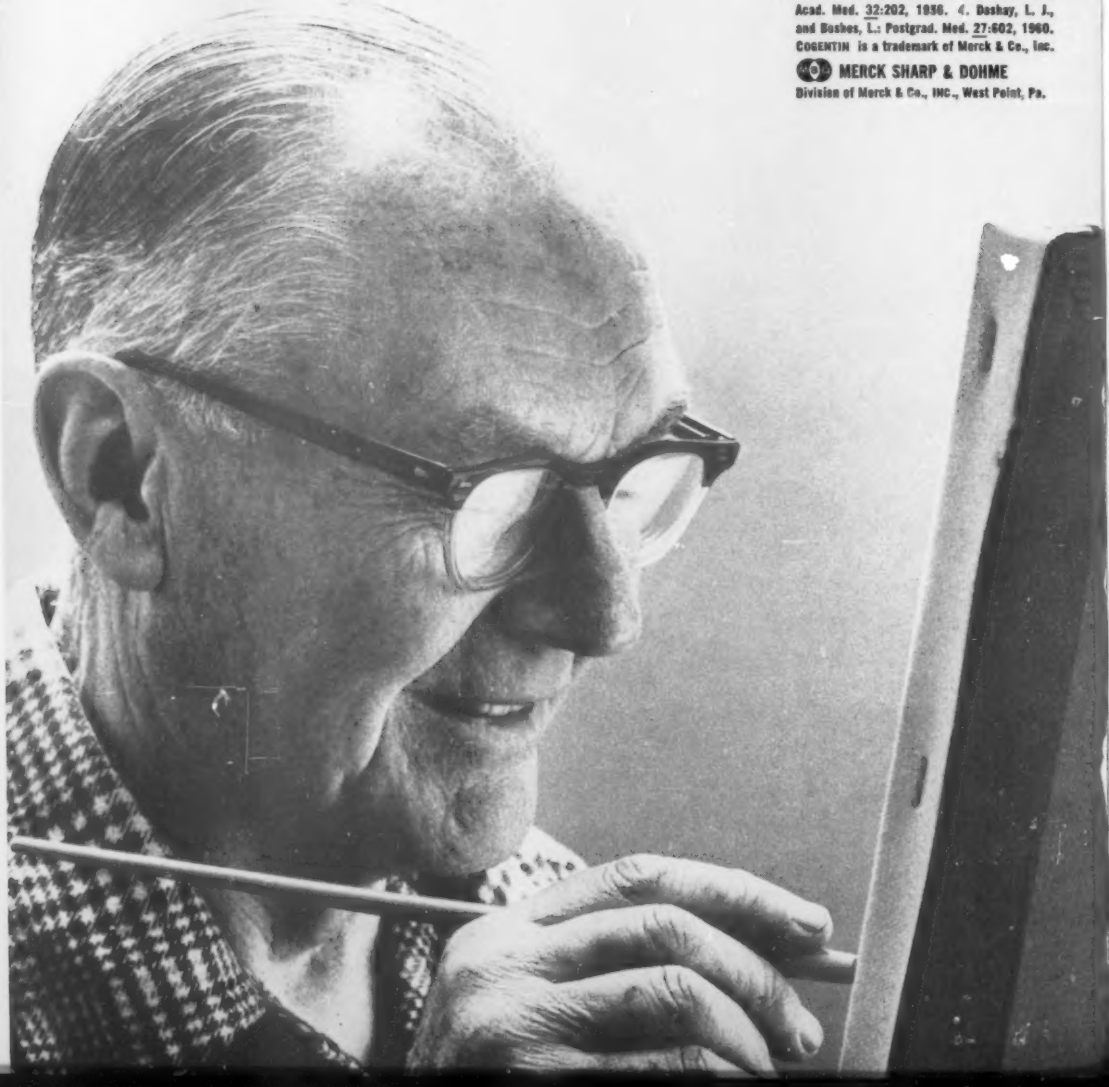
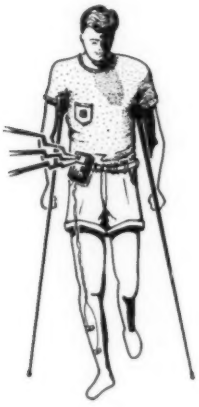


Announcing

Meditron's new and unique

EMG MUSCLE TRAINER

. . . MEDITRON's newest aid for the physician with patients undergoing muscle rehabilitation after poliomyelitis, stroke, or other nerve and muscle lesions.



dimensions
3 x 5 x 1¾ inches

MEDITRON's Muscle Trainer is a miniaturized, all-transistorized, single-ended, battery-operated EMG with an audio output to a built-in loudspeaker (earphone optional).

In bed, sitting up, or walking around, the patient may have the Model MT beside him or carried suspended from a shoulder strap or fastened to a belt. He may be connected to the instrument by any of a variety of surface, needle, or imbedded wire electrodes.

Like any EMG, the Model MT detects clinically invisible muscle action potentials. The encouragement the patient receives when he hears the results of his mental efforts even before he can see or feel any muscle movement, will keep him working, focus his efforts on the right muscle, and speed up his rehabilitation.

Economically as well as technically unique, the Model MT provides this invaluable help at a fraction of the cost of tying up a full-size EMG for the purpose.

Write, wire, or telephone Dept. N for price lists, and for specifications on MEDITRON's electromyographs, stimulators, and other specialty and research electronic instruments.

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in depression

Nardil..."practical, efficacious, and safe ...for general use..."*

Effective in psychotic depressions and non-psychotic depressive states with less than 2% reported significant side effects

Clinical studies show that Nardil is potent enough for the most severe depressive conditions and yet safe enough for the office treatment of mild depressive states. With Nardil, relief of depressive symptoms has been consistently reported in 70 to 80% of office patients and 60 to 70% of hospitalized patients...with a less than 2% reported incidence of significant side effects. This excellent clinical history plus the added benefits of a simple dosage schedule and significantly greater economy make Nardil well suited for the treatment of most depressive states.

Full dosage information, available on request, should be consulted before initiating therapy.

*Sargant, W.: *Brit. M. J.*, p. 225-227, (Jan. 28) 1961.

Nardil®

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P814